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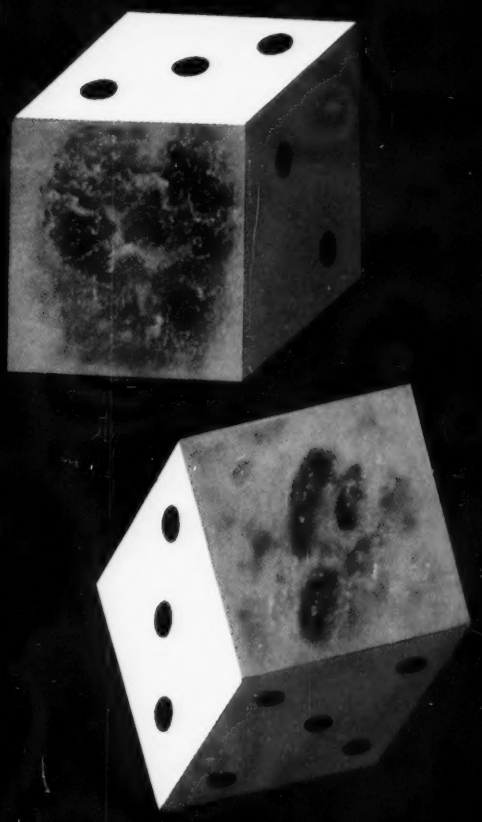

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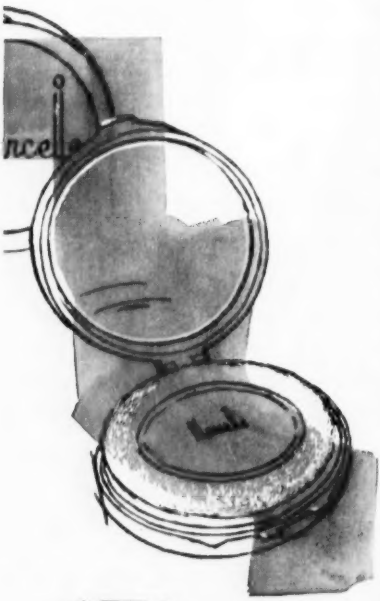

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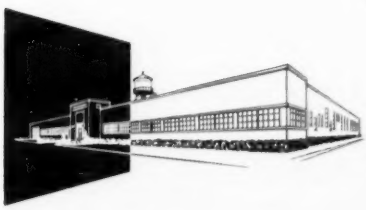

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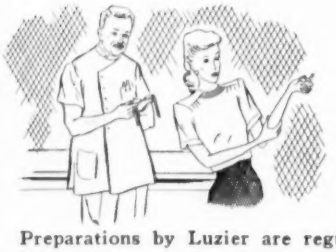

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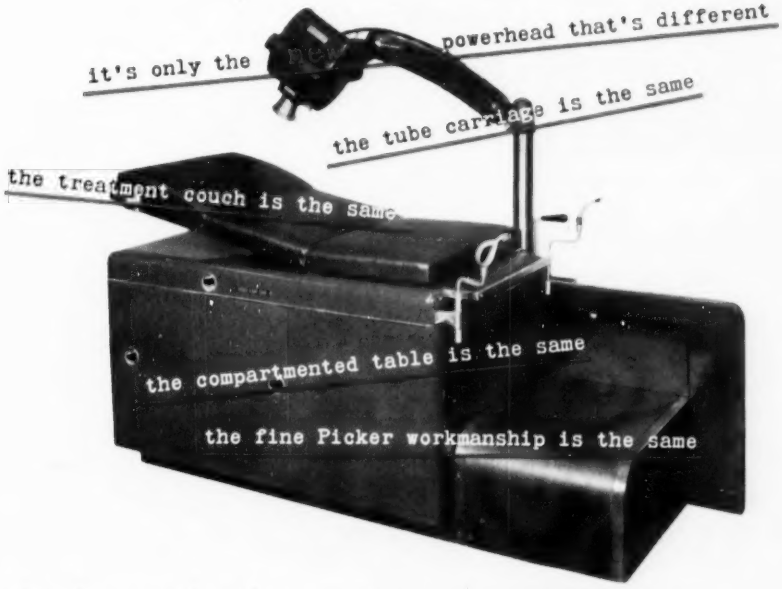
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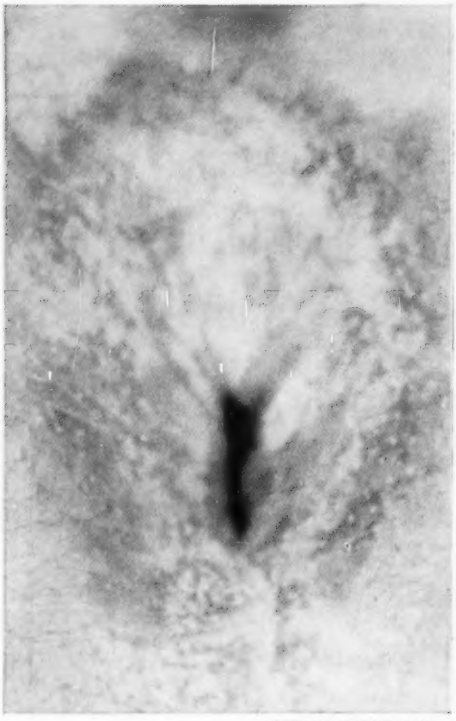

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*Alexander, R. M. and Manhein, S. D., *J. Invest. Dermat.* **21**: 223-225, October 1953.

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PIGMENT AND PIGMENT TUMORS

BIOCHEMICAL BASIS OF HUMAN MELANIN PIGMENTATION

THOMAS B. FITZPATRICK, M.D., Ph.D.
AND
AARON BUNSEN LERNER, M.D., Ph.D.
PORTLAND, ORE.

RESEARCH on the biochemistry of melanogenesis can be divided historically into three periods.[1]

1. The identification of tryosinase, in 1895, by Bertrand and Bourquelot in certain varieties of mushrooms.

2. The demonstration of "dopa oxidase" in human skin, in 1917, by Bruno Bloch and the elicitation of some of the chemical steps in the conversion of tyrosine to melanin, in 1920 to 1930, by Raper. Bloch and his collaborators believed that dopa oxidase was found to occur specifically in mammalian skin. Raper carried out a thorough study of the intermediate reactions involved in the conversion of tryosine into melanin by tryrosinase in plants and meal worms. During this period there was a vigorous controversy over the mechanism of melanin formation in man, since tyrosinase could not be demonstrated in mammalian tissue. Human skin contained an enzyme which could catalyze the oxidation of dopa to melanin, but dopa had not been shown to occur in mammalian tissues.

3. The rediscovery of tyrosinase activity in mammalian melanomas by Hogeboom and Adams, in 1942, and the beginning of the present era of studying the enzymatic processes underlying melanin formation in mammals. Following this discovery, Greenstein, and later Lerner, Fitzpatrick, Calkins, and Summerson, in 1949, showed conclusively that extracts from human, mouse, and horse melanomas contain both tyrosinase and dopa oxidase activities. Further studies by Lerner, Fitzpatrick, Calkins, and Summerson presented evidence for a single-enzyme hypothesis to account for melanin formation in mammalian tissue. These authors suggested that the term dopa-oxidase be abandoned in favor of the single term tyrosinase to describe the enzyme involved in the oxidation of both tyrosine and dopa to melanin. The demonstration of tyrosinase in human skin, in 1950,[2] provided the first concrete evidence that tyrosine could act as a precursor in human melanin formation.

From the Department of Dermatology, University of Oregon Medical School.

Read in the Symposium on Pigment and Pigment Tumors before the Bronx Dermatological Society, Dec. 18, 1952.

Previous reports have presented various phases of melanin metabolism, including a discussion of biochemical factors which control the tyrosine-tyrosinase reaction,[3] evidence suggesting certain differences in tyrosinase activity between normal human pigment cells and pigment-cell neoplasms,[4] and, finally, clinical studies of the control of melanin pigmentation by chemical agents.* In the present review a discussion of the biochemical basis of normal pigmentation and selected pigmentary disturbances in man will be presented. An attempt will be made to explain disturbances of melanin pigmentation in certain diseases on the basis of altered biochemical factors affecting melanin formation within the melanocyte.

In order to understand the interplay of various factors in the process of melanin pigmentation, it is necessary to review our present knowledge of the chemical nature of melanin, the site of melanin formation, and the biochemical reactions involved in the production of melanin by the pigment cell.

NATURE OF MELANIN

The term melanin is used to denote various shades of brown and black pigments occurring naturally in mammals, insects, plants, and marine animals. Melanin pigments result from the polymerization of oxidation products of orthodihydroxyphenyl compounds to insoluble substances of high molecular weight. In human metabolism these orthodihydroxyphenyl compounds are formed from the oxidation of tyrosine, and it is likely that the only dihydroxyphenyl compound giving rise to melanin in man is dihydroxyphenylalanine (dopa). Because numerous brown and black pigments occur in human tissues (nervous system, adrenal medulla, etc.) it is necessary to define human melanin on a cytologic as well as on a chemical basis. Hydroxytyramine, arterenol (nor-epinephrine), epinephrine, and small quantities of dopa are orthodihydroxyphenyl compounds that have been isolated from the adrenal medulla,[7] and the melanin pigments resulting from the oxidation of these substances in the medullary cells should be differentiated from the melanin found in the pigment cells of the skin and eyes. Therefore, melanin can be defined as an insoluble brown or black pigment formed by the enzymatic oxidation of tyrosine by tyrosinase attached to mitochondria in the cytoplasm of pigment cells in the skin and uveal tract. Melanin derived from mammalian tissue is always bound to a protein. When melanin is obtained from a dihydroxyphenyl compound other than dopa, the name of the compound should be used as a prefix to melanin, e. g., epinephrine melanin.

SITE OF MELANIN FORMATION

In a recent study,[8] when whole mounts of human epidermis separated from the dermis by enzymatic digestion with pancreatin were used, it was shown that certain dendritic-shaped pigmented cells in the skin were the only cells in which tyrosinase activity could be demonstrated histochemically. The pigment cells form a syncytium along the epidermal-dermal junction. Evidence from studies of human fetal skin [9] and embryological studies in lower mammals [10] indicate that pigment cells in the skin arise from the neural crest and migrate to the epidermis.

The term melanocyte was proposed recently for the mature, pigment-forming cell which formerly had been called melanoblast or melanophore.[11] The term melano-

* References 5 and 6.

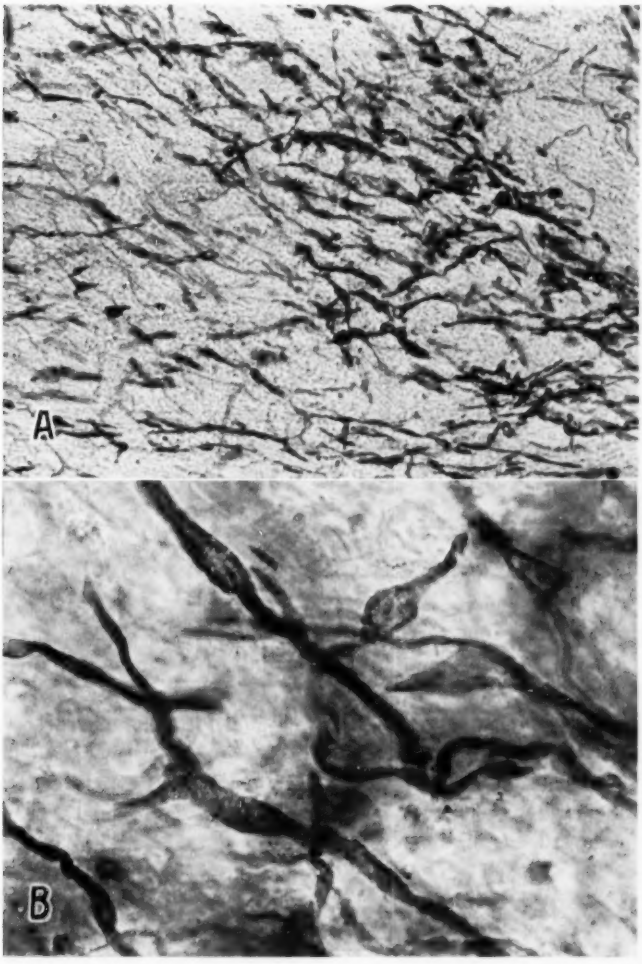

Fig. 1.—Pigment cells in the human leptomeninges. Note syncytium of melanocytes with connecting dendritic processes. This whole mount is similar to preparations of epidermis separated enzymatically and showing a syncytium of cells.[8] Leptomeningeal melanocytes represent an arrested migration of the melanoblast during its migration from the neural crest to the epidermal-dermal junction during neonatal life. Human medulla, unstained whole mount. *A*, × 100, *B*, × 600.

blast should be reserved for the immature melanin-forming cell at its origin in the neural crest, in its migration to the epidermal-dermal junction during the embryonal stage of development, or in malignant melanomas.

Melanocytes may occur in the dermis in compact cellular masses (blue nevi) or as groups of cells scattered through the dermal connective tissue (Mongolian spot). The location of melanocytes in the dermis probably represents arrested migration of the melanoblast in its course from the neural crest. Dermal melanocytes occur normally in certain primates.

Melanocytes representing arrested migration of melanoblasts are also found in the human leptomeninges. The human leptomeninges are derived embryologically from the neural crest, and it is probable that melanocytes migrate to the area of the medulla along with the pia-arachnoid. Leptomeningeal melanocytes occur on the ventral surface of the medulla oblongata and more rarely extend to the region of the olfactory bulb and the fissure of Sylvius. In general, the darker the skin color the greater the incidence of the leptomeningeal melanocytes. In Figure 1 are illustrated leptomeningeal melanocytes taken from a deeply pigmented male of Greek extraction. These cells occasionally give rise to malignant melanomas.

Under ordinary conditions melanocytes probably multiply at a slow rate. Mitotic figures have been observed only after ultraviolet irradiation of the skin. When melanocytes are destroyed by physical or chemical means, permanent depigmentation results.

BIOCHEMISTRY OF MELANOGENESIS

Melanin-Forming Enzymes

The process of melanin formation involves the conversion of a colorless naturally occurring amino acid, tyrosine, to an insoluble brown polymer. This process could be carried out in mammalian tissue only by the catalytic action of an enzyme. Although an enzyme hypothesis for human melanin formation had been postulated over 50 years ago, it was not until 1950 that an enzyme was demonstrated in human pigment cells which could oxidize tyrosine to melanin.[2] The term tyrosinase for this enzyme is preferable to the terms polyphenoloxidase, dopa oxidase, or phenolase. It is true that dopa must be present before tyrosinase can catalytically oxidize tyrosine. However, dopa itself can be readily oxidized to melanin indirectly by enzymes not involved in melanin formation, such as oxidizing agents in an active cytochrome system. This oxidation by the cytochrome system is often mistakenly referred to as a dopa-oxidase reaction. No substance is more active or abundant than tyrosine as substrate for the enzymatic formation of melanin by mammalian tissue, and tyrosinase is, we believe, the most suitable designation for the mammalian melanin-forming enzyme.

Role of Copper

Copper is an essential part of tyrosinase obtained from plant,† insect,[14] and mammalian tissues.[15] Tyrosinase in human epidermis also requires copper for its activity, since the tyrosine-tyrosinase reaction in human pigment cells is inhibited by agents which combine with copper.[2]

† References 12 and 13.

Sulfhydryl Groups and Melanogenesis

The tyrosine-tyrosinase reaction in mammalian tissue is regulated by physical and chemical factors common to many enzymatic reactions, for example, temperature, electrolyte concentration, pH, and redox potential.[3] However, a unique regulating mechanism of the tyrosine-tyrosinase reaction and of melanin formation exists for the mammalian melanocyte. It is now known that compounds containing –SH groups, such as glutathione, inhibit mammalian tyrosinase, perhaps by binding the copper in the enzyme complex.[16] Rothman, using plant tyrosinase, previously had demonstrated inhibition of the tyrosine-tryosinase reaction by –SH groups contained in aqueous extracts of human epidermis. On the basis of these studies Flesch and Rothman [16] proposed that in normal human melanocytes both substrate (tyrosine) and enzyme (tyrosinase) are present but unable to interact because of the

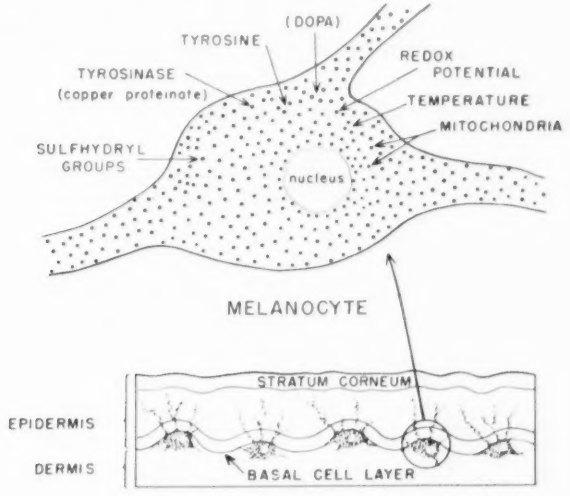

Fig. 2.—Biochemical factors controlling melanin formation.

presence of inhibitory –SH groups. Physical agents (ultraviolet rays, x-rays, radium, and infrared rays) and possibly inflammation can oxidize the inhibitory –SH groups, thereby releasing the normally inhibited enzymes. Further experimental proof of the sulfhydryl hypothesis of pigmentation must be obtained before it can be accepted as the sole explanation for the activation of human tyrosinase. Other mechanisms also appear to operate to maintain tyrosinase in an inactive state. For example, tyrosinase cannot be demonstrated in the larvae of Drosophila if the larvae are ground with sand and extracted, whereas if the larvae are previously treated with chloroform vapor, tyrosinase activity is obtained.[17] It is possible that such a protyrosinase may exist in human melanocytes. The various factors controlling human melanin formation are illustrated in Figure 2.

The existence of an inhibited tyrosine-tyrosinase system in the normal human melanocyte is not inconsistent with the facts of clinical pigmentation. If the tyrosine-

tyrosinase system were uninhibited or uncontrolled, melanin formation would proceed at a rapid rate, and all human skin would be black.

The series of reactions which occurs in the enzymatic oxidation of tyrosine to melanin is illustrated in Figure 3. It is likely that such a scheme is operating in the human melanocyte, although all the intermediates in this reaction have not been isolated during enzymatic catalysis by tyrosinase obtained from human sources. One of the intermediates, 5,6-dihydroxyindole, has been isolated from the urine of a patient with a metastatic melanoma and melanuria.[18]

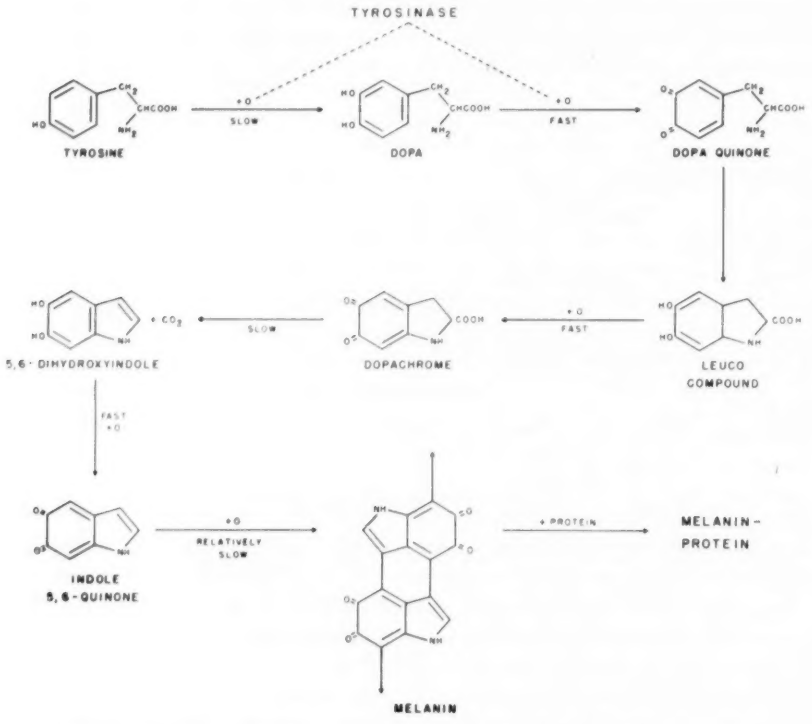

Fig. 3.—Enzymatic oxidation of tyrosine to melanin by mammalian tyrosinase.

Inhibition of Human Melanin Formation

Numerous in vitro inhibitors of the tyrosine-tyrosinase system have been developed which block the series of reactions by interfering directly with tyrosinase activity or with one of the intermediate compounds in the conversion of tyrosine to melanin.[1] Although several of the various in vitro inhibitors have been shown to produce depigmentation in animals, only a few are known to affect human melanin formation.

Organic Sulfur-Containing Compounds.—Thiouracil, given to a patient with generalized malignant melanoma and melanuria, has been shown to decrease the

concentration of melanin precursors in the urine.[19] In a Negro patient under treatment with thiouracil for hyperthyroidism, areas of depigmentation developed.‡ Prolonged administration of dimercaprol (BAL) resulted in the graying of hair in a patient being treated for chronic arsenical intoxication. It is probable that compounds containing sulfhydryl groups block the formation of melanin by limiting the availability of copper necessary for tyrosinase activity.

Parahydroxyphenyl Compounds.—Three parahydroxyphenyl derivatives, hydroquinone, monobenzylether of hydroquinone, and parahydroxypropiophenone, are effective inhibitors of mammalian melanin formation.[20] Only the two latter compounds have been used clinically to inhibit melanin formation. Monobenzylether of hydroquinone may be converted to hydroquinone in the human skin. Hydroquinone and parahydroxypropiophenone inhibit the enzymatic oxidation of tyrosine to dopa, which is the first step in the conversion of tyrosine to melanin (Fig. 3). A clinical and experimental study of monobenzyl-ether of hydroquinone and *p*-hydroxypropiophenone as therapeutic depigmenting agents in man has been reported previously.[5] Although depigmentation is not always obtained with monobenzylether of hydroquinone, a recent study of 84 patients with pigmentary disturbances treated with monobenzylether of hydroquinone showed a good therapeutic result in 76% of patients treated.[21]

Reducing Agents.—Ascorbic acid acting as a reducing agent decreases melanin pigmentation in man by two mechanisms. First, ascorbic acid prevents the further oxidation of dopa quinone, and melanin cannot be formed by the action of tyrosinase on tryosine until all the ascorbic acid is oxidized. Second, ascorbic acid reduces the melanin in the skin to a relatively light-colored substance. Large doses of ascorbic acid have been reported to decrease pigmentation in patients with Addison's disease.[21] Administration of ascorbic acid by iontophoresis has been shown to decrease the skin color in berloque pigmentation.[22]

Large-scale clinical screening of known effective inhibitors of in vitro melanin formation has not been carried out as yet. It is possible that by such a study new inhibitors of melanin pigmentation may be developed. At the present time, monobenzylether of hydroquinone is the most effective inhibitor of melanin formation clinically.

PHYSIOLOGIC VARIATIONS IN MELANIN PIGMENTATION

Melanin pigmentation of the skin reflects the content of melanin in epidermal melanocytes and varies from total absence (albinism) to black (Negro and other pigmented races). The net content of melanin in the melanocyte depends on a balance of melanin formation and melanin excretion from the pigment cell. At the present time little is known regarding the mechanism of melanin excretion. Two routes of excretion have been described. The first is through the dermis via the lymphatics to the lymph nodes and into the venous circulation and ultimately into the urine. In patients with Addison's disease and in Negroes, melanin is often found in the liver and spleen and in the epithelium of Henle's loops and collecting tubules of the kidney.[23] The second path of excretion occurs through the epidermis. In

‡ Hellerstein, H. K.: Personal communication to the authors.

heavily pigmented skin (in the Negro and in Addison's disease) melanin granules are routinely observed in the stratum corneum. Much investigation remains to be done on the physiologic turnover of melanin in the melanocyte. The increased pigmentation of Negro skin could be explained in part on the basis of an altered rate of formation and excretion of melanin. A difference in the physiologic turnover of melanin between melanocytes in white skin and in Negro skin is apparent in the rate and degree of depigmentation after local application of inhibitors of melanin formation. Application of monobenzylether of hydroquinone to normal Negro skin often produces complete depigmentation. In white skin, depigmentation occurs only in skin which is pathologically hyperpigmented, as in Addison's disease or lentigo. Normal white skin is not depigmented by local applications of monobenzylether of hydroquinone. Since monobenzylether of hydroquinone is known to affect melanin formation, these differences of response in Negro and white skin may be related to a more rapid excretion rate of melanin in the melanocyte in Negro skin.

It is likely that melanogenesis in the human melanocyte occurs physiologically in "spurts," since it is not possible to demonstrate in vitro melanin formation from tyrosine in normal skin. Certain physiologic factors, such as hormones and exposure to ultraviolet radiant energy, serve to activate the tyrosine-tyrosinase system within the cytoplasm of the melanocyte so that melanin formation results. The degree of response to these stimulating influences will vary in a given melanocyte depending on the various controlling factors which are operating at the time. Among the factors controlling melanin formation, as shown in Figure 2, the tyrosine, dopa, and oxygen concentrations, and the temperature and pH would be expected to be approximately the same for normal persons. The concentrations of tyrosinase and sulfhydryl groups are likely to vary in different persons and to depend in large part on genetic factors. Except in albinism, which will be discussed below, it is not possible with our present knowledge to conclude which of these specific factors controls the rate of melanogenesis in human skin.

PITUITARY CONTROL OF HUMAN MELANIN PIGMENTATION

Clinical conditions and physiologic states associated with increased activity of the pituitary gland, such as pregnancy, Addison's disease, and acromegaly, frequently exhibit an increase in melanin pigmentation. Decreased pituitary function, as in panhypopituitarism, is associated with a relative decrease in melanin pigmentation. On the basis of these well-known clinical facts, it was postulated [1] that a pituitary-adrenal axis exists, similar to the pituitary-thyroid axis, whereby adrenal hormones inhibit the release of a pigment hormone from the pituitary gland. In primary adrenal insufficiency, e. g., Addison's disease, a compensatory hyperactivity of the pituitary, with an increased output of the pigment hormone, would result and cause an increase in melanin synthesis. In adrenal insufficiency secondary to pituitary hypofunction, an increase in the pigment hormone could not occur, despite the absence of adrenal cortex inhibition. The first evidence supporting this hypothesis came from observations of patients treated with corticotropin and cortisone. Hyperpigmentation was found to occur in a patient treated with corticotropin for arthritis.[1] It was not known whether or not the pigmenting hormone present in the corticotropin as a contaminant was directly related to the increased pigmentation. Recent clinical studies with hog pituitary fractions containing relatively high concentrations

of melanocyte-stimulating hormone (MSH) and negligible amounts of corticotropin have been made in normal subjects. Prolonged parenteral administration of these pituitary fractions rich in MSH has produced generalized melanin hyperpigmentation.[24]

Also, it has been observed that administration of cortisone and hydrocortisone to patients with Addison's disease decreases the hyperpigmentation. These hormones have recently been shown to inhibit the release of MSH from the pituitary gland.[24]

The demonstration of MSH activity in the urine in various conditions known to be associated with increased pigmentation,[23] e. g., Addison's disease and pregnancy, and the production of generalized melanin hyperpigmentation in humans following administration of MSH [24] appear finally to establish pituitary MSH as an important factor in the control of human melanin formation.

INBORN ERRORS OF METABOLISM OF PHENYLALANINE AND TYROSINE AND ASSOCIATED PIGMENTARY DISTURBANCES

Phenylalanine and tyrosine are present in almost all dietary proteins and probably represent the sole source of the aromatic nucleus in human metabolism. Apparently the body cannot synthesize the aromatic nucleus. Unless phenylalanine, an essential amino acid, is present in the diet of young rats, growth does not occur. Normally, metabolic requirements for tyrosine are fulfilled from the conversion of phenylalanine to tyrosine and from tyrosine in the diet. In a strict sense, one might conclude that phenylalanine, rather than tyrosine, is the precursor of melanin formation. The various metabolic pathways of phenylalanine and tyrosine are shown in Figure 4. Phenylalanine is metabolized in two directions, either undergoing an oxidative deamination to form phenylpyruvic acid or an oxidation of the ring with insertion of an hydroxyl group. The latter step is carried out by an enzyme present in liver. Tyrosine is metabolized at different sites in the body to three biologically important compounds. In the thyroid, tyrosine is iodinated and ultimately forms thyroxin. In the adrenal medulla and probably in the chromaffin system, tyrosine is converted to epinephrine and arterenol. In melanocytes tyrosine is converted to melanin. In addition to forming the three compounds mentioned above, tyrosine undergoes oxidative deamination to parahydroxyphenylpyruvic acid, and later another hydroxyl group is inserted into the ring. Rearrangement then occurs, forming 2,5-dihydroxyphenylacetic acid or homogentisic acid. In the normal person homogentisic acid is degraded with the opening of the benzene nucleus and the formation of acetoacetic and fumaric acid. The two latter compounds are then converted to carbon dioxide and water.

Four diseases are associated with metabolic blocks at various points in the metabolism of phenylalanine and tyrosine (Fig. 4). Of the four diseases the following three are associated with pigmentary changes in the skin: decreased melanin formation in phenyluria, absence of melanin formation in albinism, and deposition of a brown pigment in cartilage and skin in alcaptonuria.

The similarity of structure of epinephrine (3,4-dihydroxyethanolmethylamine) to dopa (3,4-dihydroxyphenylalanine) has led to much speculation regarding the role of epinephrine in human melanogenesis. Bloch's original investigations [26] were

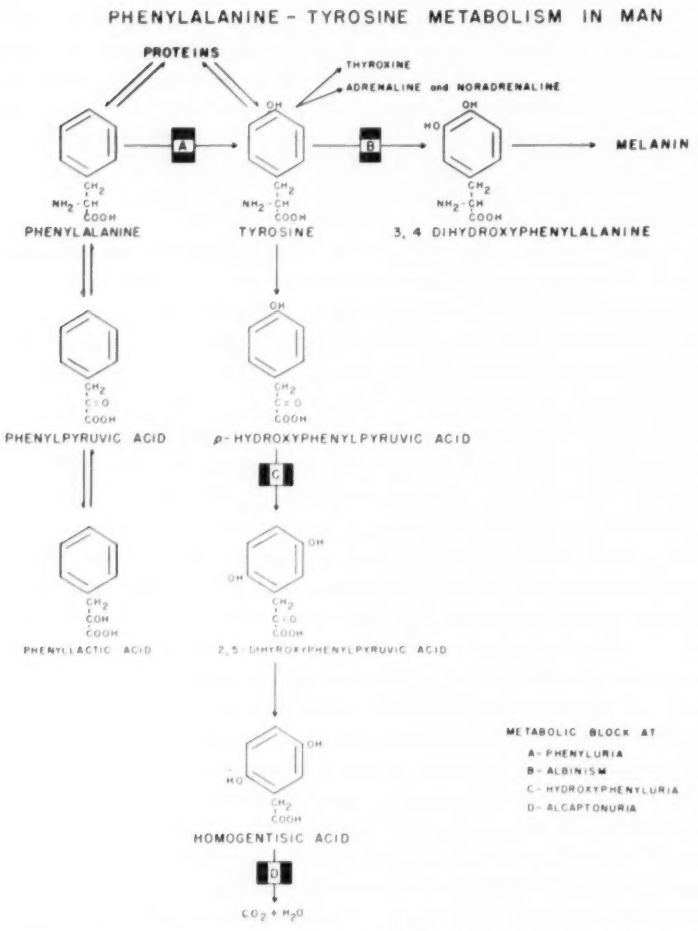

Fig. 4.—Intermediary metabolism of phenylalanine and tyrosine, illustrating four metabolic "blocks."

based on the fact that "the strongest hyperpigmentations of the skin combined a lesion of an organ whose main product is a pyrocatechin derivate, adrenalin. For this reason, I experimented with the cyclic amino acid which is most closely related to adrenalin, that is, 3,4-dioxyphenylanin, which for the sake of convenience I call D-O-P-A." Recent in vitro studies with the tyrosine-tyrosinase reaction indicate that epinephrine is probably not involved in human melanogenesis. Mammalian tyrosinase does not catalyze the oxidation of epinephrine to melanin.[27] Epinephrine, unlike dopa, cannot act as an accelerating factor in the oxidation of tyrosine by mammalian tyrosinase.[27]

Phenyluria

Phenyluria (also known as phenylpyruvic oligophrenia or phenylketonuria) is a recessive trait characterized by mental deficiency, increased excretion of phenylpyruvic acid, phenyllactic acid, and phenylalanine in the urine, and abnormally high phenylalanine levels in the blood. Patients with this disease characteristically have fair hair, blue eyes, and a blond complexion.

The metabolic block in phenyluria has been established by Jervis[28] to involve the formation of tyrosine from phenylalanine. Patients with phenyluria must therefore obtain all their tyrosine requirements from dietary sources. Since tyrosine requirements of the body are largely obtained from the conversion of phenylalanine to tyrosine, phenyluric patients suffer from a relative tyrosine deficiency. Reduced tyrosine levels have been reported in the blood in phenyluria.[29] The decrease in pigment found in phenyluria is therefore probably a consequence of the inability to convert phenylalanine to tyrosine rather than a result of the failure in conversion of tyrosine to melanin, as in albinism. This explanation is further suggested by the fact that phenyluric patients are able to tan only slightly. The limited availability of the melanin precursor, tyrosine, is the most likely explanation of the reduced melanin content of the skin of patients with phenyluria. To prove this hypothesis, it would be desirable to administer large quantities of tyrosine to these patients in order to determine the effect on pigmentation and other clinical findings.

Albinism

Albinism has been estimated to occur in the general population in a ratio of 1 : 5,000 to 1 : 25,000. In a recent summary, Falls ¶ has presented a classification of albinism. A modified form of this classification is as follows:

Generalized Albinism

1. Complete
   - (*a*) total or nearly total lack of melanin in the hair, skin, and eyes
   - (*b*) recessive hereditary pattern
2. Incomplete
   - (*a*) ability to produce a minute amount of melanin with increased melanin formation with advancing age
   - (*b*) recessive and irregular dominant hereditary pattern
3. Albinoidism-leucism
   - (*a*) very light hair and skin, no nystagmus or photophobia, good vision, blue iris
   - (*b*) increasing pigmentation of hair, skin, and eyes with advancing age
   - (*c*) autosomal dominant hereditary pattern

¶ Personal communication to the authors.

Localized Albinism

1. Cutaneous
   (*a*) unilateral linear areas of depigmentation, often following the distribution of a cutaneous nerve
   (*b*) remains throughout life without progression or repigmentation
   (*c*) dominant hereditary pattern
2. Ocular
   (*a*) may involve the entire eye or the fundus only
   (*b*) head-nodding, nystagmus, usually defective vision, blue to brown iris, some iris translucency

Until recently, the inability of the albino to form melanin was attributed to an absence of melanocytes in the skin and eyes. It has been shown [8] through the use of special stains that albino skin contains as many melanocytes as normal white skin. Hence, it is likely that albinism represents a genetically determined inability to convert tyrosine to melanin. Single genes appear to regulate single steps in a biochemical reaction through the control of enzyme synthesis. The existence of albinism is good evidence for the role of enzymatic processes in human melanogenesis. If human melanin formation occurred by any means other than through enzymatic processes, we would expect it to occur in albino tissue.

Histochemical studies of albino skin have failed to demonstrate tyrosinase in the albino melanocytes.[8] Other known factors which control melanin formation, such as sulfhydryl groups and redox potential, have not been studied in human albino skin. Serum and hair copper determinations were recently carried out on five patients with generalized incomplete albinism. The values as presented in the Table are within normal limits.

It is not surprising that copper levels in albino hair are within the normal range. Copper has been shown to function in the formation of keratin.[31] Since keratinization is not impaired in albinos the copper content of hair would be expected to be slightly low or within normal limits. The copper levels of albino hair have approximately the same range as normal blond hair.

From a clinical standpoint, albinism is primarily an ophthalmological problem. Nystagmus, errors of refraction, and reduced visual acuity often severely incapacitate the albino. Occasionally, patients with albinism seek medical advice for help in decreasing their intolerance to sunlight. A rational treatment of albinism consists of supplying the deficient enzyme, tyrosinase, prepared from human sources. This has proved to be impractical because tyrosinase is a protein and is therefore antigenic. Also, it is not possible with existing techniques to introduce agents into the epidermis by injection. Attempts to decrease the ultraviolet sensitivity by local application and oral administration of compounds which absorb ultraviolet light may be a more practical approach to the problem. Preliminary studies with oral administration of 8-methoxypsoralen to albino patients indicate that the marked sensitivity to ultraviolet is reduced and the patients are able to tolerate direct sunlight.[9] This substance absorbs a wide range of the ultraviolet spectra, from approximately 2,200 A. to 3,400 A. units.

Although the clinical features and genetics of albinism have been thoroughly studied, there are no reports on metabolic studies. A study of the blood and urine

of albinos after ingestion of large quantities of tyrosine may reveal the presence or absence of certain intermediates in the tyrosine to melanin reaction as compared with normal persons.

The various factors which cause increased melanin pigmentation in normal persons do not affect albinos. In pregnancy, albinos fail to develop the usual pigmentation of the areolae of the nipples. Addison's disease has not been reported in albinism. There are no records of malignant melanomas occurring in albinos, although squamous-cell carcinomas of the skin have been reported. It it were possible to study a statistically significant number of albinos and prove that the expected incidence of melanomas did not occur, it might have some bearing on the relationship of melanin formation and malignant melanomas. At the present time it is thought by some investigators that melanin formation may have little or no relationship to the problem of malignant melanoma. These persons offer as evidence for this belief the fact that nonpigmented so-called amelanotic melanomas are as malignant as deeply pigmented ones.

*Serum and Hair Copper Determinations in Albinos**

Age	Sex	Serum Copper (γ per 100 Cc.)	Hair Copper (Dry Weight) (γ per 100 Cc.)
15	F	100	2.3
38	F	143	1.6
42	M	100	...
30	M	135	2.2
35	M	100	2.3
Normal range		45-175	1.5-2.5

* Copper determinations were made using a modification of Nielsen's method.[80]

Alcaptonuric Ochronosis

Alcaptonuric ochronosis is a rare recessive trait characterized by a triad of clinical findings—black urine, pigmentation of the cartilaginous tissue, and arthritis. Alcaptonuria literally means the occurrence in the urine of a substance which has "an affinity for alkali." This term arose from the fact that the urine of patients with alcaptonuria undergoes a rapid spontaneous oxidation in the presence of alkali. The urine contains 2,5-dihydroxyphenylacetic acid or homogentisic acid.

In alcaptonuria normal degradation of homogentisic acid does not occur, and the compound accumulates in the extracellular fluid, where it is oxidized to a brown or black pigment. Homogentisic acid, for some as yet unknown reason, selectively localizes in cartilage. Normal cartilage placed in a colorless solution of homogentisic acid gradually darkens to a black color. The fibrous connective tissue surrounding the cartilage does not darken. This phenomenon explains the black cartilage which is a cardinal feature of alcaptonuric ochronosis.

It should be emphasized that homogentisic acid is an intermediate in the catabolism of tyrosine by normal patients and does not accumulate in the extracellular fluid because it is converted to carbon dioxide and water. In alcaptonuria, homogentisic acid accumulates because of the absence of an enzyme which normally brings about its degradation. The gene controlling the synthesis of this enzyme is therefore lacking in alcaptonuria.

Black Urine.—The urine is of normal color when freshly voided, but gradually turns black upon exposure to air owing to the autooxidation and polymerization of homogentisic acid to a black insoluble pigment. Homogentisic acid is a strong reducing agent and will reduce Benedict's solution. However, the positive Benedict's reaction in alcaptonuria produces a rather characteristic dirty-red or orange color, and technicians can be trained to recognize this unique color and thereby discover alcaptonuria in routine urinalysis. Because of the reduction of Benedict's solution these patients are occasionally treated as diabetics. Homogentisic acid is easily differentiated from glucose because of its lack of optical activity and failure to undergo a fermentation reaction.

Pigmentation in Ochronosis.—The black pigment in ochronosis is noted clinically in cartilaginous tissue. The black cartilage appears through the skin as a blue color

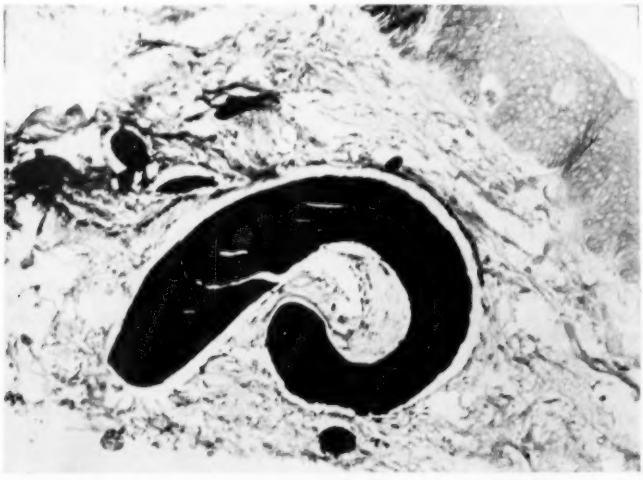

Fig. 5.—Deposition of polymerized homogentisic acid in the skin of patient with alcaptonuric ochronosis. Pigment does not darken with silver nitrate, but turns an intense black with polychrome methylene blues. Paraffin section, × 115.

due to the Tyndall scattering phenomenon. An early sign of alcaptonuric ochronosis is a blue discoloration of the ears, especially of the concha and antihelix, and later the tragus and antitragus. Triangular brown pigmentary deposits with their bases toward the cornea are noted in the sclerae. Bluish discoloration of the tendons of the hands also occurs. Pigmentation of the skin is an uncommon finding. In a patient of Laymon's # studied by us, a peculiar blue reticulated pigmentation was noted in the skin of the face, neck, upper chest, and dorsum of the hands. Biopsy of these lesions was carried out, and the pigment was studied histologically and histochemically. In Figure 5 there is noted a bizarre annular deposit of amorphous brown ochronotic pigment. This pigmentary deposit did not darken with

Studied through the courtesy of Drs. Carl Laymon and Allan Dixon, Department of Dermatology, University of Minnesota Medical School, Minneapolis. Some of the material in this section has been included in a report, "Ochronosis," by Carl Laymon, M.D.

Becker's silver stain for melanin and therefore does not have the same reaction as melanin pigment stained with this technique. The brown pigment changed to an intense black color when stained with polychrome methylene blue. The histochemical reaction for tyrosinase in the specimen was negative both in the epidermal melanocytes and in the pigment mass itself. The pigment in alcaptonuric ochronosis represents a polymer of 2,5-dihydroxyphenylacetic acid, similar to the brown pigment in the adrenal medullary cells, which is a polymer of oxidized epinephrine or arterenol. This latter pigment, like ochronotic pigment, does not darken with Becker's silver stain for melanin.

Arthritis.—A peculiar gait, kyphosis, and a stooping posture are characteristic features of long-standing alcaptonuria. These changes are due to the presence of osteoarthritis in the vertebrae. It is believed that the arthritis results from primary erosion of the articular cartilages containing ochronotic pigment.

SUMMARY

The biochemical basis of normal melanin pigmentation and selected pigmentary disturbances in man is presented.

Human melanin is defined as a brown or black pigment formed by the enzymatic oxidation of tyrosine by tyrosinase contained in the cytoplasm of pigment cells located in the skin and uveal tract.

Histological and histochemical studies are cited as evidence for the belief that melanin is formed only in certain dendritic-shaped cells, melanocytes. Although not definitely proved in man, evidence from embryological studies in lower mammals indicates that melanocytes are derived from the neural crest.

The process of melanin formation in man is shown to involve the conversion of a colorless, naturally-occurring amino acid, tyrosine, to an insoluble brown polymer. This biochemical process is carried out by the catalytic action of a copper-containing enzyme, tyrosinase. The tyrosine-tyrosinase reaction is controlled primarily by naturally occurring sulfhydryl compounds in the epidermis, although the redox potential and availability of tyrosine may be limiting factors.

Inhibition of human melanin formation is noted following the ingestion of two organic sulfur-containing compounds: thiouracil and dimercaprol (BAL). Locally applied parahydroxyphenyl derivatives, including monobenzylether of hydroquinone and parahydroxypropiophenone, can cause depigmentation of Negro skin or hyperpigmentation of white skin.

Pituitary regulation of human melanin formation is suggested by the occurrence of pigmentation in patients receiving corticotropin (ACTH) containing melanocyte-stimulating hormone (MSH) as a contaminant. MSH activity is now known to be present in the urine in various conditions associated with increased melanin pigmentation.

Pigmentary disturbances are associated with blocks in the intermediary metabolism of phenylalanine and tyrosine. Decreased pigmentation in phenyluria (phenylpyruvic oligophrenia) occurs because of a relative deficiency of the melanin precursor, tyrosine. Lack of melanin pigment in albinism is related to the absence of the enzyme tyrosinase in the melanocytes. The explanation of albinism on the basis

of absence of melanocytes is not valid in view of recent studies which show melanocytes to be present in albino skin. Alcaptonuric ochronosis is associated with the deposition of a brown pigment in cartilaginous tissue and rarely in the skin. This pigment does not have staining properties similar to melanin contained in melanocytes and probably represents polymerized homogentisic acid.

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HISTOGENESIS AND CLINICOPATHOLOGIC CORRELATION OF NEVI AND MALIGNANT MELANOMAS

Current Status

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WE FEEL rather privileged to have been asked to participate in a symposium held by dermatologists. We are general pathologists, but it is abundantly clear that many of the key contributions to the understanding of the histologic nature of pigmented tumors have been made by dermatologists, especially by those great and pioneering dermatologists, Unna and Bloch. However, it must also be evident that the problems of nevi and malignant melanomas transcend party lines, as you obviously agree, and it would be well if this example were followed frequently and bilaterally. Certainly, there is no place for professional chauvinism in the interpretation of scientific data.

This presentation is concerned, first, with a recapitulation of clinicopathological impressions based on data from a recent study of these lesions at the Memorial Cancer Center [3] and, secondly, with a fairly detailed ledger and evaluation of the evidence for the major concepts of their histogenesis.

When we tried to determine the basic reasons for some of the difficulties that have been encountered in the histological diagnosis of nevi and malignant melanomas, it appeared to us that the confusingly wide range of histologic variations of these lesions had not been fitted, and apparently could not be fitted, into a practical, orderly parallel with the neural concept of their genesis.[2] On the other hand, we found the concept of the epidermal or epithelial origin of nevi and melanocarcinomas—apart from what we * and others before us † have believed to be its accuracy—especially useful in the creation of diagnostic criteria which the pathologist could grasp and apply. It seemed to us that with the help of this reorientation, the pathologist, with his routinely stained slides, would be able to see, to understand, and to appraise the nevi and melanocarcinomas with a degree of accuracy and confidence to which the neurogenic theory did not appear to lend itself. There is gratifying evidence that within recent years the pathologist has done just that, with a resulting effective improvement in the diagnostic standards. For this improvement, all concerned with the diagnosis and therapy of these lesions are to be credited.

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† References 5 to 8.

One of the essential aids to an understanding of these variously named benign and malignant lesions is a classification that gives prognostic and other clinical meanings to sharply defined histological patterns. This is the aim of the following classification [3]:

Benign	Malignant
(*a*) Junctional nevus	(*a*) Melanocarcinoma
(*b*) Compound nevus	1. Superficial
(*c*) Intradermal nevus	2. Deep
(*d*) Blue nevus	(*b*) Malignant blue nevus
(*e*) Juvenile melanoma	

The details of the histology of the benign lesions, which have been described elsewhere, need not be repeated here except for certain controversial or often misinterpreted features. These will be mentioned only briefly, and reference may be made to the source of their documentation.[3] In addition, as mentioned, we shall include some of the essential clinical information derived from a recently completed study of 934 cases of malignant melanomas.[3] These comprised three groups: in one, the histological slides of the primary tumor and adequate follow-up study were available in 337 cases; in a second group of 286 cases, the follow-up data but no slides of the primary tumor were available, and in a third group of 311 cases, the five-year follow-up studies were not recorded or accessible.

NEVI—GENERAL CONSIDERATIONS

Although, in our opinion, the junctional nevus (Fig. 1*C*) or the junctional component of the compound nevus (Fig. 1*D*) is the forerunner of all malignant melanomas of the skin and mucous membranes (the rare malignant blue nevus excepted), it does not by any remote implication follow that all junctional nevi become cancers. Fortunately, only a very small percentage of them—a percentage obviously impossible to calculate accurately with available data—undergo malignant change. Nevertheless, because the moles on the palms, soles, and genitalia are in practically every instance junctional nevi, or have a junctional component in the form of compound nevi, it would appear to be wise preventive therapy to remove, when feasible, all such moles, in these areas, preferably prior to puberty. With regard to the intradermal nevus (so-called "common mole") there is no evidence that it is ever the source of a malignant melanoma. However, despite statements to the contrary in textbooks, it simply is not always possible to know clinically if a given lesion is an intradermal, compound, or junctional nevus except, for practical purposes, in the three locations previously mentioned. The presence of a tuft of hair protruding from the mole is a fairly reliable indication that the lesion is an intradermal nevus, whereas the lack of elevation of a mole suggests that it is a junctional nevus. But since certainty rather than gambling odds, however great, is the aim, it would seem that histological examination of the lesions treated affords to date the only method of achieving that aim.

Compound Nevus

The compound nevus, according to our definition,‡ consists of a junctional nevus overlying an intradermal nevus to which, we believe, the junctional nevus originally gave rise (Fig. 1*D*). Some dermatologists use the terms "combination," "combined,"

‡ References 1 and 2.

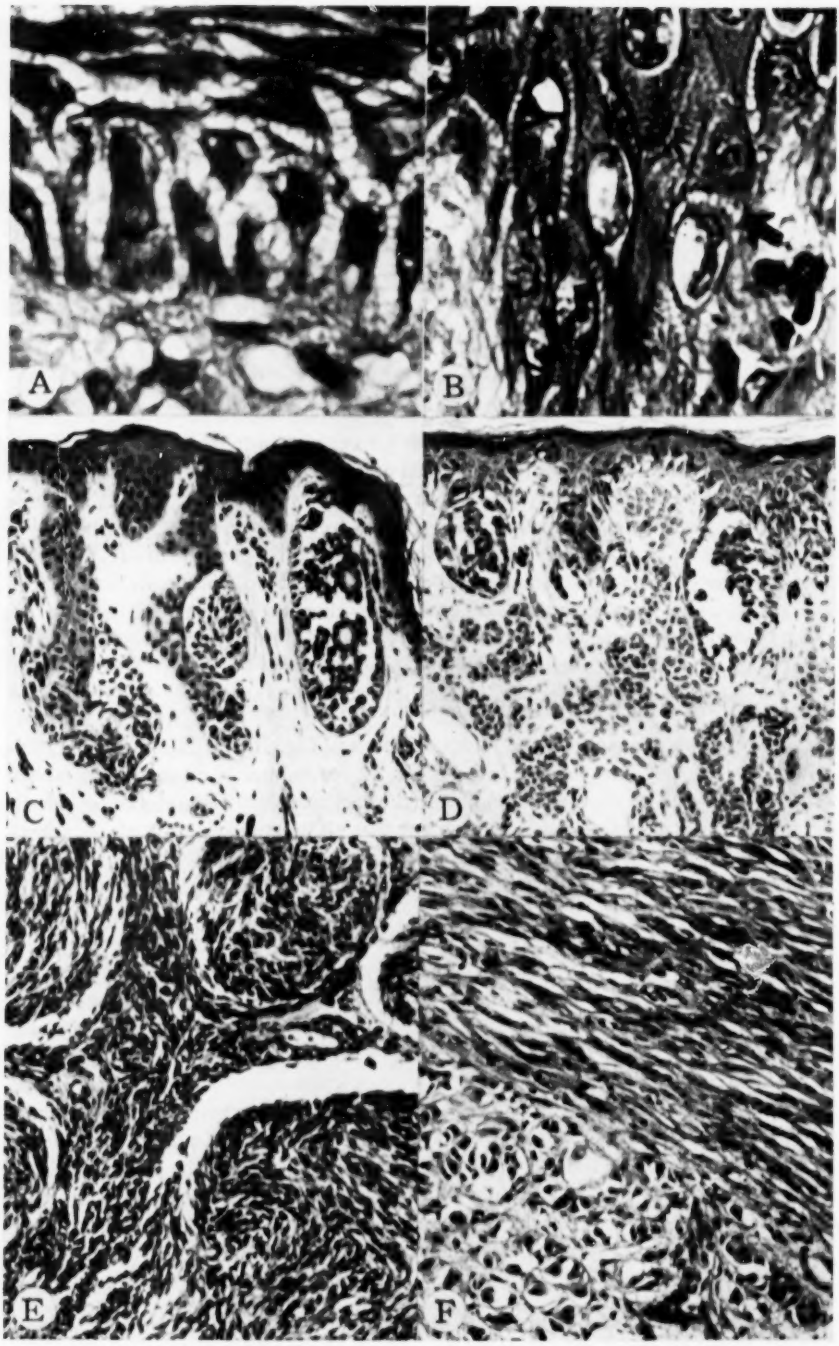

Fig. 1.—*A*, Intercellular bridges of basal cells and overlying cells of stratum spinosum. *B*, "clear cell" (*cellule claire*) of stratum germination (arrow) with prickles at its superior and lateral borders, indicative of origin from a modified basal cell. *C*, junctional nevus, entirely intraepithelial by definition, and showing the characteristic loss of cohesion of epithelial cells of which the nevus is composed. *D*, compound nevus, made up of a junctional nevus and an underlying intradermal nevus. *E*, cellular blue nevus, frequently mistaken for a malignant blue nevus. *F*, malignant blue nevus, illustrating the benign-appearing portion in the upper part of the photomicrograph and a fairly obviously malignant area in the lower. Hematoxylin and eosin stain.

or "mixed nevus" to indicate any combination of nevi. Actually, inasmuch as compound nevi, as so defined, occur in about 98% of children [4] and in about 12% of adults,‡ whereas other combinations are infrequent, and inasmuch as the interpretation of the compound nevus embodies the concept of the evolution of the intradermal nevus ("common mole") and also has special clinical meaning by virtue of its constant junctional element, it has seemed to us that the designation "compound nevus" as herein defined has somewhat more substance that the multivalent "combination nevi." Incidentally, the term "intraepithelial nevus" serves no clear purpose inasmuch as it is applied variously and confusingly to junctional nevi, "lentigines," incompletely formed seborrheic keratoses, pigmented and nonpigmented acanthoses, and even intraepithelial basal-cell carcinomas. Moreover, it would help further to relieve confusion if "lentigo" and "lentigo malignum" were abandoned. Their precise histological meaning has not been made clear, and so they are variously used to indicate junctional nevus, activated junctional nevus, and superficial melanocarcinoma.

Malignant Blue Nevi

There is a widely prevalent impression that blue nevi do not become malignant. In the past, most of the lesions presumed to be malignant blue nevi were in reality (1) what we have termed the "cellular blue nevus," (Fig. 1*E*) occurring usually about the buttocks, (2) spindle-celled melanocarcinomas in which the origin from junctional nevi had been overlooked, (3) spindle-celled epidermoid carcinomas of the kind which may follow radiation therapy, and (4) sclerosing angiomas with abundant hemosiderin. However, there remain a few cases that are truly examples of cancerous transformation of blue nevi (Fig. 1*F*). We have collected six such cases, two of which had been submitted from outside sources for review. In three of the six instances, metastases had occurred; two have been followed for only a short period of time. The presence of adjacent histologically benign-appearing residue of the blue nevus and the absence of epidermal junctional change associated with the tumor are part of the diagnostic requirements. The cells of the malignant portion as well as the metastases may be spindled but have the features of anaplasia. In addition, necrosis is common in the primary lesion, and many foci may appear epithelial in pattern although there is no suggestion that blue nevi are epithelial in origin. Unlike the other pigmented nevi, the blue nevi are most likely neural.

Juvenile Melanomas

One of the most remarkable of the lesions under study is the juvenile melanoma. It had long been appreciated that there were lesions of children which, although diagnosed as malignant by the pathologist, nevertheless failed to metastasize. The analysis of the microscopic appearance of these tumors, which was first made in 1948,[4] served not only to segregate them histologically from the usual pigmented nevi of childhood but also to establish a basis of comparison of the clinical behavior and diagnostic criteria of related lesions of both adults and children.[4] It is now clear that, notwithstanding their morphologic resemblance to the fatal melanocarcinomas of adults, approximately two-thirds of the juvenile melanomas may be diagnosed for what they are entirely on the basis of their histological features, as previously defined.§ This fact is of great practical importance because we now know from

follow-up studies that apparently a small percentage of juvenile melanomas may persist into adult life and retain their histological landmarks.[3] Such benign lesions, in the past, have automatically been called malignant on the basis of the arbitrary fact that the patient was past the age of puberty. Of somewhat less importance is the revelation that such benign lesions—relatively few in number—have been inadvertently counted as cured malignant melanomas. Briefly, the recognition of the juvenile melanoma of children and of adults is based on an evaluation of several features, including superficially located Touton-like or myogenous-appearing giant cells, edema, and telangiectasis of the upper cutis, sharply delimited compact epidermal-appearing clusters of nevus cells, a rather characteristic form of spindling of the cells, a frequently associated abundant inflammatory reaction, mostly of lymphocytes, and, of course, the presence of the components of a compound nevus || (Fig. 2, *A* and *B*).

Melanocarcinomas of Children

As stated, about two-thirds of the juvenile melanomas may be recognized microscopically; the remaining third are histologically indistinguishable from the adult melanocarcinomas. In the latter cases, the prepubertal age of the patient dictates the diagnosis of juvenile melanoma. In addition, there remain isolated instances in which true, potentially metastasizing or fatal melanocarcinomas occur in children of various ages. We have accumulated five such cases—two from other institutions—so that the incidence of this complication is exceedingly small. In each instance the histological picture was different on two principal counts from that of any of the benign juvenile melanomas just referred to. In the first place, none of the morphologic characteristics of the juvenile melanomas were present. In the second place, these malignant lesions of childhood exhibited a distinctive anaplasia categorically greater than was present in the benign juvenile melanomas. A third feature might be added for one of the varieties of melanocarcinomas of childhood, namely, the marked simulation of a deeply pigmented epidermoid carcinoma (Fig. 2, *C* and *D*).

The question as to what happens to the juvenile melanomas in later life cannot be answered directly, in the absence of data on partially excised lesions. However, we do have inferential evidence on this matter. In a certain number of primary cutaneous melanocarcinomas of adults there are residual traces of juvenile melanomas just as there may be noted traces of an ordinary compound or junctional nevus at the margin of a melanocarcinoma. It is impossible to know precisely what percentage of juvenile melanomas eventually become cancerous in adult life, but our impression is that they are no more or less liable to become melanocarcinomatous than are other compound nevi.[§]

Of course, many as yet unanswerable problems arise in connection with the juvenile melanomas. It is still to be determined if these cells, which may be morphologically indistinguishable from the melanocarcinoma of adults are different from them physiologically. Or is the endocrine milieu of the prepubertal child a barrier against the invasiveness of these cells? The proved capacity of a maternal melanocarcinoma to metastasize through the placenta into the fetus strongly suggests that the endocrine status is a potent factor in the receptivity of the tissues of the fetus to the propagation of melanocarcinomatous cells, inasmuch as the hormonal pattern of the newborn is similar in important respects to that of the mother. Moreover, it

§ References 3, 4, and 9.

|| References 3, 4, and 9.

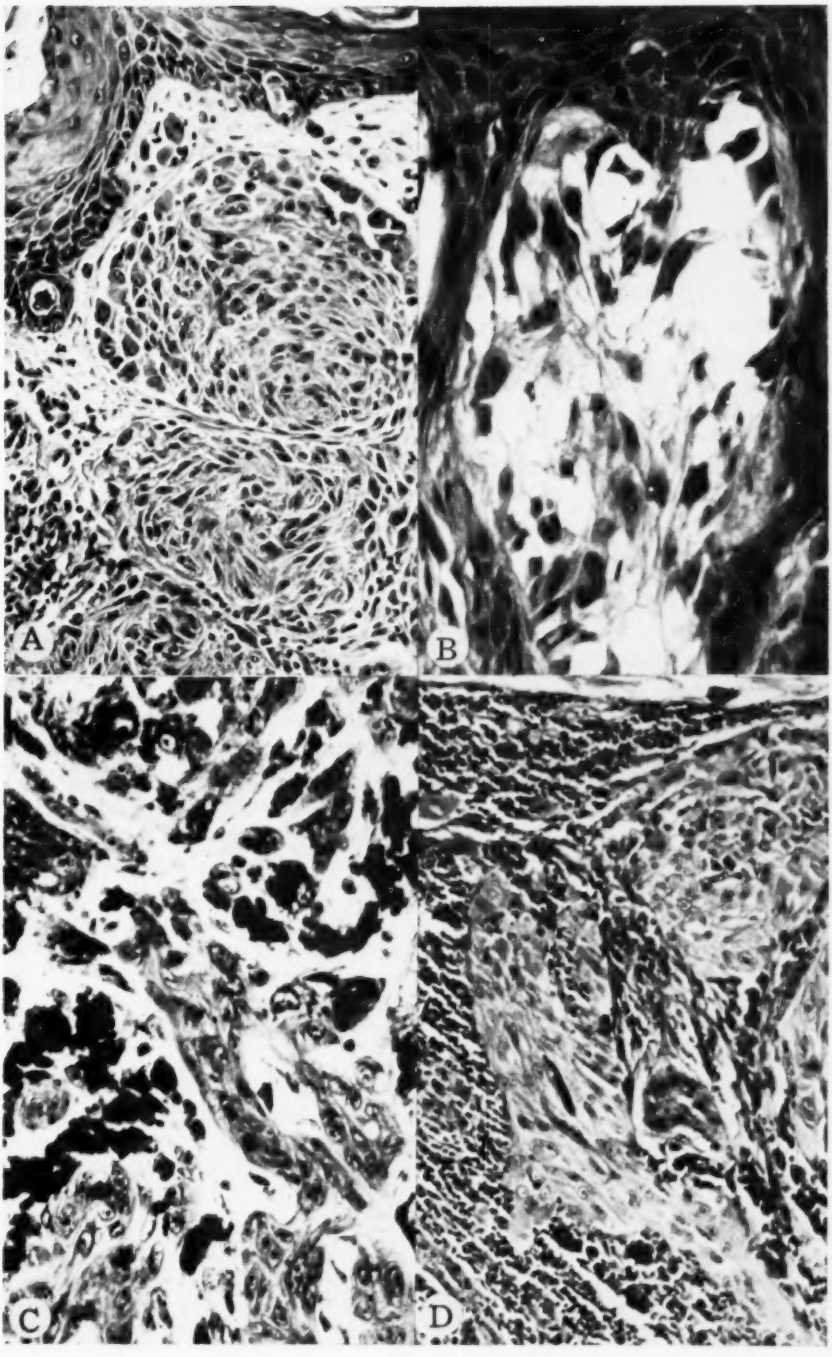

Fig. 2.—*A* and *B*, juvenile melanomas of childhood, quite benign in behavior, illustrating the components of the compound nevus, the compact epithelial-like clusters (*A*), the lack of pigmentation, the giant cells, and the superficial edema and telangiectasis (*B*). *C*, primary melanocarcinoma of childhood. This and the very few other metastasizing melanocarcinomas of childhood are histologically distinguishable from the benign juvenile melanomas. *D*, metastasis to a lymph node from the melanocarcinoma illustrated in *C*. Hematoxylin and eosin stain.

would seem relevant to investigate intensively the hormonal status of those few children of intermediate ages between birth and puberty who develop metastasizing melanocarcinomas, as well as of those adults who retain the histological landmarks of juvenile melanomas. The occurrence of primary melanocarcinomas in the newborn has been recorded at least twice, but in each instance there was basis, in our opinion, for questioning the histological diagnosis.¶[3]

PROGNOSTIC INDICES

In an attempt to determine if there were any histological features which permitted prognostic differentiation of the malignant melanomas, statistical evaluation was made of such factors in the primary lesion as surface area, depth, location, ulceration, pleomorphism, mitotic figures, and pigment content, as well as age and sex of the patient. These data are tabulated in detail elsewhere.[3] In brief summary, they indicate, as anticipated, that those lesions of greater size, depth, ulceration, pleomorphism of cells, and mitotic figures were, as a group, linked with higher fatality rates than the lesions in which these features were less prominent. The pigment content was of no use as a prognostic index, and, also, on this basis, we should anticipate that the determination of the quantity of tyrosinase present in melanocarcinomas would be equally useless prognostically. As a further corollary to the lack of correlation between pigment content of melanocarcinomas and prognosis, it is pertinent to refer to the anticipation of some investigators that inhibition of tyrosinase activity might possibly serve as a means of therapeutic attack against melanocarcinomas. However, it would appear that not only the lack of correlation between pigment content and prognosis, but also the lack of correlation between the content of many other enzymes and prognosis in other tumors, such as alkaline phosphatase and osteogenic sarcomas, and acid phosphatase and rectal and prostatic carcinomas, unfortunately offers little ground for such therapeutic enthusiasm. This is by no means to infer that the tenable hypothesis advanced by Figge in 1941 [10] and since adopted by others, namely, that the "positive dopa reaction indicates the presence of inhibited tyrosinase," should not be thoroughly studied from all points of view.

The influence of the age of the patient has already been mentioned in connection with the prepubertal group. Beyond this period, there seemed to be no really significant differences in survival rates among males, except for a not unexpected sharp decline after the age of 70. Among the females, the poorest results were noted in the third and fifth decades. Of special interest, however, is the difference in the survival rates of men and women. Of the series comprising 337 cases in which we had the opportunity to examine the histological slides of the primary lesions, 38.8% of the women with malignant melanomas survived, whereas only 18.2% of the men survived. These differences are statistically significant.[3] The difference in survival of the sexes is particularly striking, with lesions of the skin of the head and neck region in which the percentage of survivals for women was 57.5% as opposed to 23.3% for men.[3]

¶ After the submission of this manuscript, we observed at the Memorial Cancer Center the case of a 5-year-old Negro with a primary melanocarcinoma of the buccal mucosa. In addition, the child had an androgenic adrenal cortex carcinoma, which caused an abnormally high level of urinary 17-ketosteroids. The anaplastic primary focus of melanocarcinoma almost disappeared after the administration of ethinyl estradiol (Estinyl), which, however, did not appear to have affected the widespread metastases found at autopsy.

MELANOCARCINOMAS OF MUCOUS MEMBRANES

Of all the anatomical locations the mucous membranes of both the head and neck region and the genitalia and anorectal regions yielded the worst prognosis by far. The delay in reaching a diagnosis as a result of the paucity of symptoms or of misinterpreted histological patterns, as well as the difficulties in the surgical control of some of these areas, is in part responsible for the graver outlook from the therapy of mucosal melanocarcinomas. Precisely the same criterion for the diagnosis of primary melanocarcinomas of skin applies to those of mucous membranes, namely, the evidence of origin from a junctional nevus. The absence of melanin in the tumor cells is not a reliable basis for excluding the diagnosis of mucosal melanocarcinoma, because the pigment is absent in about half the cases. In our series of 337 cases in which adequate follow-up study and the histological slides were available for our review, 51, or 15.1%, originated in the mucous membranes of the nasal cavity, accessory nasal sinuses, lips, buccal mucosa, tongue, tonsil, larynx, bronchus, anorectal region, labia minora, clitoris, introitus, urethral meatus, and glans penis.[3] A primary melanocarcinoma of the esophagus was found also, but the patient was included in our "indeterminate series" of cases because of the limited follow-up period. Very recently, we observed an example of a melanocarcinoma of the uterine cervix.

MULTIPLE PRIMARY MELANOCARCINOMAS

The application of the criterion of the differentiation of primary from metastatic melanocarcinomas is of considerable prognostic importance. It is obviously a much better situation if a small cutaneous lesion is proved to be a second primary melanocarcinoma rather than a metastasis from the original primary tumor. On this basis, it was found that in 12 (3.6%) of 337 cases there were multiple primary melanocarcinomas.[3] In one instance, there were seven such tumors, and the patient was alive and free of disease 20 years after the first lesion was discovered and 17 years after the last. This predisposition of a patient with a malignant melanoma to develop multiple melanocarcinomas is a statistically significant phenomenon. We emphasize this point because we have noted that in patients with melanocarcinomas there occurs a diathesis for the development of junctional nevi as if there were some circulating humoral factor which was activating such nevi and, in a meaningful percentage of cases, leading to the formation of multiple melanocarcinomas.

The tendency for patients with melanocarcinomas to develop active junctional nevi accounts in some measure for so-called "local recurrences." Surgeons often blame themselves for local recurrences on the assumption that they remove too narrow a margin of tissue about the tumor. Of course, this assumption is warranted in those instances in which the tumor or even peripheral junctional activity reached the margins of resection and no additional excision was carried out. However, we have the impression[3] that in a number of instances junctional activity is provoked at the margins of excision after the tumor has been removed, and that grafts particularly must be viewed with this possibility in mind. Systematic studies of this practical matter are clearly indicated, particularly from the point of view of the determination of the degree of predisposition to junctional change present in the skin in the vicinity of a malignant melanoma.

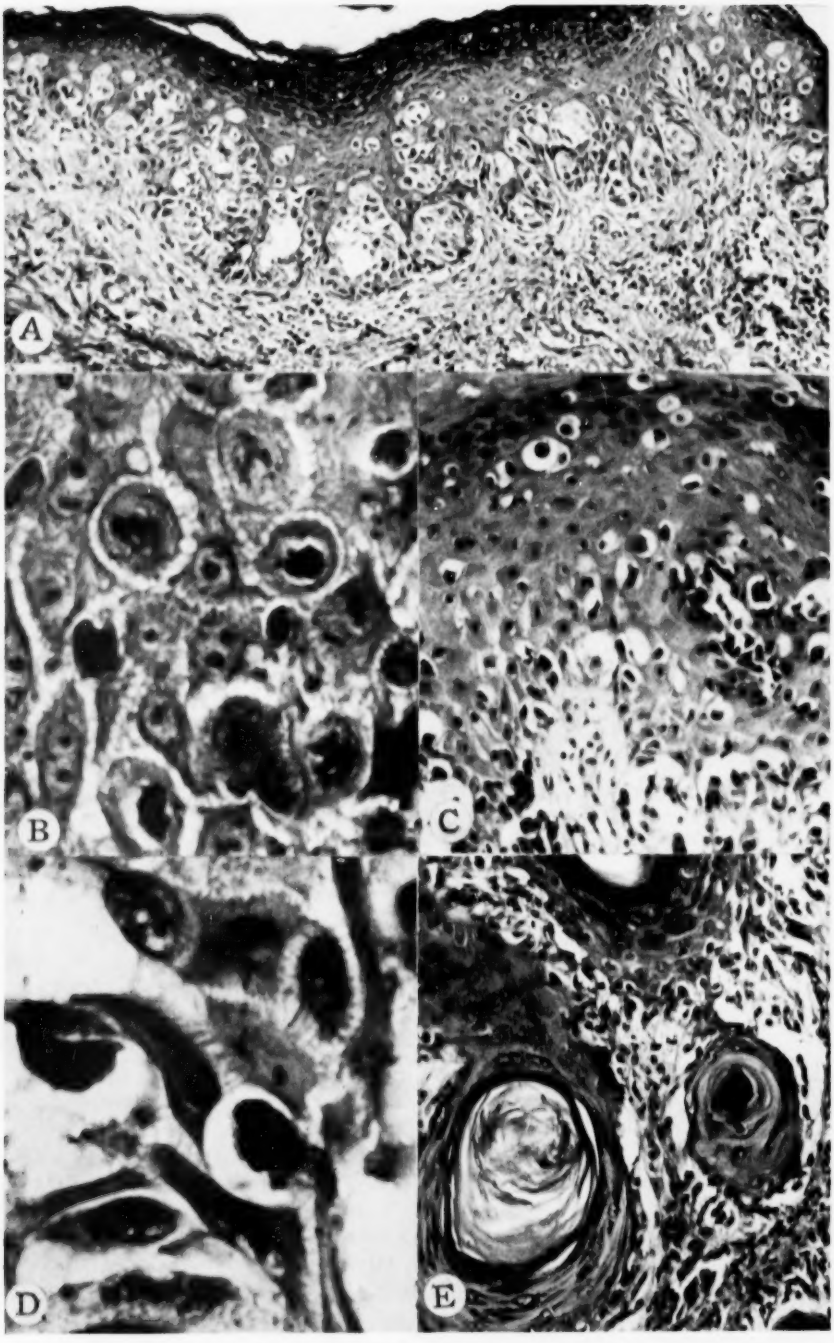

Fig. 3.—*A*, superficial melanocarcinoma with a histological pattern commonly mislabeled mammary or extramammary Paget's disease. *B*, active junctional nevus illustrating the origin of the tumor cells, several of which have abnormal mitotic figures, from the epidermal cells. The nature of the tumor cells is clearly evident from the residual prickles. *C*, rapidly fatal superficial melanocarcinoma from the ankle, again demonstrating the origin of the tumor cells from the altered, epidermal cells of all layers of the rete Malpighii. *D*, tumor cells from the intraepidermal portion of the primary melanocarcinoma of *C*, illustrating stages in the evolution of these cells from true, epidermal cells. In several of the neoplastic cells, the prickles have not yet been lost. *E*, melanocarcinoma showing a small part of the epithelial hyperplasia which is an intrinsic component of the primary lesions and is occasionally mistaken for squamous-cell carcinoma. Hematoxylin and eosin stain.

SUPERFICIAL MELANOCARCINOMAS

Of all the characteristics of the primary melanocarcinomas one of the most important prognostically is the depth of infiltration into the stroma. On the basis of this feature, we have classified melanocarcinomas into two types: (*a*) superficial, and (*b*) deep. The superficial melanocarcinoma, as indicated, refers not to the surface area, which is usually small, although it may be large, but specifically to the presence of minimal evidence of invasion. In other words, whereas the diagnosis of melanocarcinoma cannot be properly made without evidence of invasion of the cutis or submucosa, that evidence may consist merely of several subepithelial clusters of cells or even several isolated cells (Fig. 3, *A* and *C*). The analogous criterion would be that used for the differentiation of a superficially infiltrating squamous-cell carcinoma as opposed to leucoplakia or Bowen's disease (epidermoid carcinoma in situ of skin) on the one hand, and an obvious more deeply infiltrating carcinoma on the other. Usually there is ancillary evidence of activation in the form of isolated, haloed, pigmented or nonpigmented, pagetoid cells scattered throughout the epidermis and a lymphocytic reaction in the upper cutis. Approximately 10% of the melanocarcinomas are of this superficial variety. When they involve the skin, their prognosis is appreciably better than that of the deeper tumors, inasmuch as the survival rate is about 74% among the former (20 of the 27 cases). We were unable to distinguish histologically the superficial melanocarcinomas which proved fatal from those which were survived. Moreover, in three of the patients surviving their superficial melanocarcinomas, melanocarcinomatous metastases had developed in the regional lymph nodes, so that the documentation of their malignancy can hardly be doubted.[3]

Superficial melanocarcinomas occur also in mucous membranes, but here again, as with the other melanocarcinomas of mucous membranes, the prognosis is almost uniformly bad. It must be emphasized that the histological distinction between a "superficial" and a "deep" melanocarcinoma is dependent on a small additional increment of depth of invasion.

EXTRAMAMMARY PAGET'S DISEASE

The superficial melanocarcinomas are frequently mislabeled "extramammary Paget's disease," an entity about which there is some question as to its existence (Fig. 3 *A*). Other lesions commonly mistaken for so-called extramammary Paget's disease are superficial squamous- or basal-cell carcinomas, Bowen's disease, Queyrat's erythroplasia, and metastatic adenocarcinomas in which the metastatic foci are closely applied to or are actually within the epidermis. In the presence of a proved rectal adenocarcinoma, it would seem especially hazardous to postulate, as has been done in some reports, that an adenocarcinomatous lesion of the anal canal or perineum was extramammary Paget's disease and that the adenocarcinomatous metastasis of an inguinal lymph node came not from the coexistent rectal adenocarcinoma but from the so-called extramammary Paget's disease. The pagetoid melanocarcinomas tend to grow downward into the dermis along the ducts of the sweat glands and may also involve the coil glands so as to simulate a primary adenocarcinoma of sweat-gland origin. However, these tumors do not metastasize as adenocarcinomas, as would be expected of true Paget's mammary or extramammary disease. We have also seen central necrosis of nests of primary or metastatic epidermoid carcinomas and melanocarcinomas mistaken for the acini of adenocarcinomas. Moreover, activated junctional nevi or superficial melanocarcinomas

of the nipple area may be mistaken for mammary Paget's disease which, indeed, may be so closely simulated that it would be a wise safeguard if evidence were required of involvement of the immediately underlying mammary ducts by Paget's disease before that diagnosis was made histologically.

PSEUDOEPITHELIOMATOUS HYPERPLASIA

One of the findings we did not fully appreciate in our earlier studies was the almost consistently evident acanthosis and pseudoepitheliomatous hyperplasia in the melanocarcinomas.[3] This reaction is not present in the malignant blue nevi. As is well known, the presence of pseudoepitheliomatous hyperplasia occurs also in association with other tumors, particularly granular-cell myoblastomas, but in these tumors the epithelial change is possibly the expression of an irritative phenomenon and is not an intrinsic histogenetic part of the neoplasms. In the case of melanocarcinomas, it is our impression that the epithelial overgrowth plays an intimate and active part in the actual growth of the malignant melanoma in the sense that the pseudoepitheliomatous foci, as they undergo junctional change at their margins, are a major and continuous source of renewed supplies of melanomatous cells, which are dropped off from the winding, reticulated pegs into the adjacent dermis. This feature, in addition to furnishing another increment in the evidence for the epidermogenesis of the melanocarcinomas, merits study from the objective of the biochemical inhibition of growth of these tumors through a neutralization of what, in our view, is one of the sustentative elements of melanocarcinomas (Fig. 3 *E*).

THERAPY

It is generally believed that a malignant melanoma is an almost uniformly fatal neoplasm. While the prognosis is always grave, some remarkable survivals or apparent cures have been achieved, and, what is more remarkable, such good results, in a surprisingly large number of instances, have been accomplished with merely local excision.[3] This achievement has been true principally of lesions of the skin of the face and neck. Obviously much depends on the depth of infiltration and the duration of the tumor, the involvement of lymph nodes, the sex of the patient, and the location of the lesion. Although mere local excision has effected cure in a surprisingly high percentage of cases, the over-all evaluation of the results leads us to favor prophylactic regional node dissection, when feasible, in addition to the adequate excision of the primary tumor.[3] With regard to the more radical operations such as hemipelvectomies, we appreciate the need for heroic therapy in this devastating disease but we are unable to state that procedures of such magnitude have as yet been shown justifiable on the basis of statistically tested proof.[3]

Of increasing interest is the matter of prophylactic therapy. As already stated, there is adequate reason to remove the pigmented moles on the hands, and particularly on the feet and genitalia. This does not necessarily mean that the destruction of all junctional and all compound nevi in the skin of other regions of the body is a reasonable procedure. Apart from the three locations just mentioned, we should prefer to limit the removal of such nevi in areas subjected to obvious chronic irritation, even though we have no proof of the relationship of trauma and inflammation to the cancerous transformation of nevi. However, we do not regard the wholesale obliteration of numerous junctional and compound nevi without regard to their location as a measure of justifiable practicality.

HISTOGENESIS OF NEVI AND MELANOCARCINOMAS

The issue that appears to have occupied the major share of attention of workers in the field of pigmented tumors seems to have been not that of diagnostic and prognostic clarification, but rather the matter of the epithelial as opposed to the neural genesis of these lesions. Whatever the final evaluation of their histogenesis proves to be, we believe it cannot negate the more immediately utilizable clinicopathological data of the type thus far outlined in this and previous presentations. Nevertheless, because one can never gainsay the ultimate applicability of data, the problem of the precise origin of these tumors must be thoroughly pursued with a dispassionately critical evaluation of the prevalent suppositions. Moreover, the emphasis on the epithelial genesis of the nevi and melanocarcinoma appears warranted not merely because we believe this concept to be the correct one, but because, as stated previously, it appears to us—and to an increasing number of others—that this concept has facilitated an understanding of the criteria for diagnosis and of the dynamic evolution of these lesions. This section of the paper will be presented in some detail in order to try to achieve a balanced analysis of the current status of opposing thoughts.

Epithelial Origin

The essential basis for the concept of the epithelial origin of junctional nevi, compound nevi, intradermal nevi, juvenile melanomas, and melanocarcinomas has been detailed elsewhere.# In briefest terms, the positive evidence for this concept embodies the very same principle used in reaching the conclusion, for example, that the pigmented cells of the seborrhoeic keratosis (pigmented papilloma), as well as the cells of the pigmented and nonpigmented basal cell carcinomas, of Bowen's disease, of squamous-cell or epidermoid carcinomas, however anaplastic, and of other epidermal tumors, are truly epithelial in genesis. How, after all, does one decide that a given cell is an intrinsic part of the epidermis, its tumors, or, for that matter, of other structures, such as a gland? The conclusion that a small focus of epidermal carcinoma lying close to the surface is a primary squamous-cell carcinoma rather than a metastatic deposit may be safely reached, with ordinary stains, fully as well as with special stains, by the observation, as a rule, of the gradual transition of the cells of the overlying epidermis from normal-appearing to neoplastic cells. This may generally be done—as it is routinely done in many laboratories—even with epidermal carcinomas so anaplastic as to lack keratin and prickles.

It is this type of evidence which enters into the decision as to whether or not the characteristically loosened cells of a junctional nevus are truly epithelial or are, instead, nonepithelial nerve endings residing in the epithelium. There really is no difficulty at all in recognizing clearly neural intraepithelial endings such as taste buds, for example, even with the most unsophisticated of stains. The same may be said of dermal Pacinian, Krause, and Meissner corpuscles.

Differences in enzyme content or in vacuolization or in the presence of mucin, etc., do not alone make for differences in histogenesis any more than they do in the various epithelial cells of the kidney, for example. Study of the histology of normal epidermis and particularly of early or small junctional nevi, in our opinion, as well as of the intraepidermal portions of melanocarcinomas (Fig. 3 *B* and *D*), furnishes overwhelming support for this conclusion. The so-called "pagetoid" melanomas

References 1 to 4.

(Fig. 3 *A*), in which the cancerous change is for a long time entirely intraepithelial and involves practically the entire thickness of the epidermis, is an especially vivid example of evidence for the epithelial origin of melanocarcinomas. This lesion clearly represents an in situ transformation of epidermal into melanocarcinomatous cells, as evidenced, for example, even by the frequent presence of residual prickles in these tumor cells. Such prickles, which are the residua of the spines or intercellular bridges of the original epidermal cells, may also be commonly observed in the intraepidermal portion of melanocarcinomas in general (Fig. 3 *C* and *D*) and would seem to constitute irrefutable evidence of the epidermogenesis of these lesions.

If the alternate hypothesis were true—namely, that the lesions are the result of a proliferation of nerve-endings located in the basal layers, it would be difficult to explain, among other features, the melanomatous transformation often of isolated cells in all layers of the epidermis, including easily identified cells of the stratum granulosum (Fig. 3 *C*). All these facts are plausibly explainable on the basis of direct conversion of epidermal cells into junctional nevi and melanocarcinomas. Why this conversion takes the form of a melanocarcinoma rather than a basal- or squamous-cell carcinoma is the great enigma.

Special Stains

To call a clear cell of Paget's disease or Bowen's disease epidermal and an identical-appearing cell (Fig. 3 *A*)—with or without tyrosinase—of a pagetoid melanocarcinoma neural, usually simply because the metastases prove to be melanomatous, appears to us to constitute a discriminatory and arbitrarily forced application of criteria of histogenesis. The suggestion that gold, silver, and trichrome stains tell a different histogenetic story of the nevi and melanocarcinomas might be more meaningful if, at the least, what is visible in the sections stained routinely with hematoxylin and eosin were thoroughly described, interpreted, and, especially, fully compared with the corresponding cells otherwise stained. For example, there has been much warranted criticism (e. g., Bloch [7]) of the interpretation that the intraepidermal Langerhans cells, which are stained with gold preparations, are "worn out" melanoblasts. Some observers (e. g., Maximow and Bloom [11]) even doubt that they are really cells. The *lames folicaées* represent another case in point, as will be indicated further. In other words, it has seemed to us that whereas special stains in certain situations may be obviously invaluable, there is nevertheless a very real tendency for special stains in this and in other fields of morphologic investigation to create an aura of unapproachable mysticism not completely merited by the facts they disclose or sometimes obscure.

Prickles and Radioresistance.—Two of the objections which might be raised against the epidermal genesis of melanocarcinomas are first, that these tumors are radioresistant in contrast to other epidermal neoplasms and secondly, that no prickles or intercellular bridges are ever found in the melanocarcinomas. As has been previously remarked,[2] sensitivity to x-irradiation is hardly a conclusive basis for the histogenetic differentiation of tumors. For example, it is well known that occasional reticulum-cell sarcomas are resistant to irradiation although malignant lymphomas are generally sensitive and that the spindle-cell epidermoid carcinoma is radioresistant as opposed to the less virulent epidermal carcinomas. These are some of the examples that give little weight to the conclusion that melanocarcinomas can not be epidermal or epithelial in origin because of their resistance to irradiation.

The lack of prickles in the metastases or invading portions of melanocarcinomas is a more difficult issue to resolve. The reason for this disappearance of the prickles appears to us inherent in the morphogenesis of the melanomatous cell. This characteristic mode of development is best observed in an active junctional nevus or the epidermal portion overlying or at the periphery of a melanocarcinoma. Figure 3 *B* and *D* demonstrates this feature fairly well. It is seen that invariably the nevus or melanomatous cell reams its cytoplasm from the attached intercellular bridges so as to form a halo between the new cytoplasmic margin and the original cell wall. This loss of cohesion (so-called "acantholysis"), with rupture and dissolution of the prickles, is one of the basic features of these altered epidermal cells. The so-called "clear cells" (*cellules claires*), that is, the admitted melanoblasts of the basal-cell layer, are formed by a quite similar process. As a matter of fact, just as residual prickles may still be observed in the incompletely formed cell of the junctional nevus or melanocarcinoma (Fig. 3 *B* and *D*) so may they be observed occasionally even in a portion of the periphery of the clear cells of the basal layer (Fig. 1 *A* and *B*). This is to say that we regard the clear cell, as have others, not as a nerve ending or neural-crest derivative, but as a modified basal cell, and that, moreover, under certain conditions, such as after irradiation, the remainder of the cells of the basal layer may be similarly modified so as also to behave as melanoblasts or melanocytes (Fig. 1 *B*). This reference to the association of prickles with basal cells may come as a surprise, in view of the traditional notion that they lack spines. However, such intercellular bridges may be readily observed in the superior and often lateral portions of the periphery of each basal cell in normal but especially in slightly spongiotic, thinly cut sections of epithelium (Fig. 1 *A*). Moreover, they may be observed also in dopa-positive and tyrosinase-positive epidermal cells, the latter inadvertently demonstrable even in material used as evidence for the contrary viewpoint.

The new cytoplasmic wall of the cell of the junctional nevus therefore lacks the bridges and the original cell wall which are shed and which are no longer a part of the nevus cell. Hence, when these newly formed nevus or melanomatous cells divide, it is not altogether astonishing that they seem unable to regain their original capacity for recreating the delicate well-differentiated pattern of intercellular bridges. This loss of original pattern in one of the most aggressive of all neoplasms is no more surprising than the loss of the capacity to produce colloid or follicles in some of the virulent thyroid carcinomas or in the loss of cilia in other epithelial tumors. However, aggressiveness of growth cannot explain the absence of intercellular bridges in the intradermal nevi, which many now agree arise by a process of *Abtropfung* of cells from the epidermis. Still, we do not regard the failure to reproduce prickles by nevus cells—which invariably form by dislodging themselves from their outer cell wall and the connecting intercellular cytoplasmic bridges—any more reason to doubt their epidermogenesis than that the failure of ciliated epithelium, for example, of the nasopharynx to reproduce its cilia in the Schneiderian papillomas or carcinomas is evidence against derivation from such ciliated epithelium. There is still another presumptive bit of evidence that has not been previously included but might well constitute an additional phenomenon in support of the concept of the epithelial genesis of melanocarcinomas—that is, the matter of xeroderma pigmentosum and the associated melanocarcinomas. The incidence of melanocarcinomas among reported cases of xeroderma pigmentosum is approximately 3%.

Inasmuch as the incidence of melanocarcinomas among the population as a whole is about 0.018%, there is a statistically significant selective occurrence of melanocarcinomas in persons with xeroderma pigmentosum.[3] As is generally known, the cancers that have heretofore been identified with xeroderma pigmentosum have been epidermogenic, namely, basal- and squamous-cell carcinomas. The fact that melanocarcinomas also occur as a third cancerous complication of xeroderma pigmentosum is by no means proof of their epidermogenesis, but is worthy of consideration from the viewpoint that these are also epidermogenic along with the other neoplasms superimposed on this disorder.

Evidence for Neurogenic Concepts

The evidence for the neurogenesis of nevi and malignant melanomas will now be considered. An analysis of the evidence advanced for the neurogenesis of nevi and melanocarcinomas discloses a basic dichotomy of hypotheses that appears to be generally disregarded. The dichotomy is as follows: The neurogenic concept of nevi as originally advanced by Soldan, in 1899,[12] and later by Masson, in 1926,[13] and thereafter,* attributes the origin of nevi to the proliferation of cells of the Schwannian sheath. The following quotation states this point of view unequivocally: "Throughout the entire width of the nevic tissue these elements whatever their origin (epidermic or neural) show precise cytological and histogenic properties that are specific for, and characteristic of, Schwannian tissue alone" (Masson[15]).

The evidence for the concept that the nevi are derived from cells of Schwann is based almost exclusively on inferences of this type: that the epidermal melanoblasts and the *lames foliacées* of nevi are homologues of the Merkel-Ranvier corpuscles and the Wagner-Meissner corpuscles, respectively, that epidermal melanoblasts are dendritic and therefore neurogenic, and that the abundance of nerve fibrils within nevi indicate their neurogenesis.

A distinctly separate kind of evidence for the neurogenesis of pigmented cells has been accumulating since 1934, namely, that neural crest cells can be shown experimentally to influence the pigmentation of the skin and its appendages. No one doubts the validity of this conclusion, nor of the concept of the neuroectodermal origin of meningeal melanomas or of melanomas of the choroid, for example, and probably also of the blue nevus. However, there is a wide breach between this conclusion and the inference that the pigmented cells of epidermis and appendages, as well as of the nevi and melanocarcinomas, are derived from the neural crest cells—not the neural crest cells which have become organized into Schwannian sheaths or nerves, but those which have wandered singly, or in packets, to the skin, principally, but also to viscera. The evidence for these hypotheses will now be considered.

It has seemed to us that certain facts not easily reconcilable with the neurogenic concept of nevi and malignant melanomas have been either overlooked or summarily dismissed without refutatory reasons. Some of the questions which arise in connection with the validity of the concept are as follows:

1. Are the dendrites of "dendritic melanoblasts" residing within the epidermis comparable in (*a*) a tinctorial, (*b*) an anatomic, or (*c*) a functional sense to the generally recognized dendrites, of neurons of the central nervous system, for example?

* References 14 and 15.

2. Is it true that all epidermal melanoblasts are "dendritic," and is it not true that, in some instances, almost all basal cells are "dendritic"?

3. What is the significance, with regard to neurogenesis, of the loss of the "dendrites" of the "dendritic" epidermal melanoblasts when these cells drop into the dermis to form at least part of the intradermal nevi?

4. What is the source of new melanoblasts when the epidermis is lost?

5. If the epidermal melanoblasts are really nerve endings, as some state, of just what nerve structure are they the terminations?

6. Again, if epidermal melanoblasts are really nerve endings and not modified basal cells of the epidermis, why does an entire segment of the basal layer—that is, a continuous, uninterrupted row of basal cells—become pigmented in acanthosis nigricans, in Addison's disease, in scleroderma, and in other conditions? And in the pigmented seborrheic keratoses, are the component melanin-containing epithelial cells, which are admittedly melanoblasts or melanocytes, also nerve endings?

7. Is the demonstration that cells of the neural crest control cutaneous pigmentation tantamount to their actually constituting the melanoblasts of the epidermis?

8. Inasmuch as primary melanocarcinomas have been shown to arise from the nasal and oral cavities, from the larynx, the bronchus, the esophagus, and from the urethra, is it to be argued that these same pigment-forming neural-crest cells had migrated to the epithelium of these structures, simply because these organs also have nerves?

9. Finally, why are the cells of the junctional nevus considered to be neural when in most of these lesions—which are admittedly intraepithelial in location—residual landmarks of epithelial derivation, such as intercellular bridges or keratohyalin granules, may still be observed in some of the component cells, including many of the basal "clear" cells, just as they may in the known epidermal cells of Bowen's disease?

Some of the answers to these questions have already been considered in the light of the epidermogenesis of melanoblasts and nevi. However, these and the others will now be discussed in terms of their bearing on the neurogenic concept.

Migration of Neural Crest Cells

It is generally agreed that melanoblasts (so-called "dendritic" melanoblasts or melanocytes) are located within the epidermis, but it is stated that these cells are embryologically different from the adjacent epidermis in that they are presumed to be derived from the neural crest and to have migrated therefrom into the epidermis. The major support for this hypothesis is the attractive but questionable inference drawn from the control which the neural crest clearly has over the color of the skin or feathers of various animals. However, such neural control of epidermal pigmentation is as different from the actual incorporation into the epidermis of these neural cells as a *café au lait* spot is from the neurofibroma of von Recklinghausen's disease, or as an artist is from the pigments he manipulates. The fact is that no such migration into the epidermis has been demonstrated, although frequently the delicately executed neural crest explantations and related experiments of Willier and Rawles,[16] Du Shane,[17] and others have been so interpreted. Even Rawles [18] states unequivocally that "in the absence of suitable cytological criteria for recognizing pigment cells in their early unpigmented stages, their exact migratory path-

ways are not known." It has not ever been shown histologically that the neural-crest cells do, in fact, travel to and become part of the epidermis, not to mention the epithelium of such structures as the larynx, bronchus, and esophagus, as well as the cervix and vagina, in which primary melanocarcinomas may also occur. This hypothetical migration of cells of the neural crest to the epidermis is inferred from the quite separate facts that the neural crest undoubtedly influences the coloring of the epidermis and its appendages and that neural-crest cells may produce pigment in vitro. Moreover, the pigment cells of the meninges and brain and portions of the eye are also undoubtedly of neuroectodermal origin. However, there is no more reason to conclude that neural-crest cells themselves become the melanoblasts of the epidermis than to state, for example, that the papillary tall columnar epithelium of the melanin-producing ink sacs of squids, or the pigmented "cement layer" external to the epicuticle of insects, is of neural-crest origin. To conclude further, as has been done by embryologists and others from essentially this level of evidence,[18] that nevi and malignant melanomas are neoplasms of neural-crest cells is merely to widen the gap between their experimental facts and their conclusions.

The Relationship of Epidermal Melanoblasts to Other Epidermal Cells.—Perhaps labeling of neural-crest cells with a radioactive isotope may be the means eventually of clinching this phase of the issue. In the meantime, certain morphologic features of both the pigmented and the nonpigmented epidermis are irreconcilable with the neurogenesis of epidermal melanoblasts (or melanocytes). For example, it is common in a variety of situations, e. g., acanthosis nigricans, scleroderma, Addison's disease, or freckles, to observe an uninterrupted row of pigmented cells either confined to the basal layer or to this layer and the immediately overlying strata. No one disagrees that this picture represents melanin pigmentation of undoubted epidermal cells, both basal and prickle. The issue is as follows: Do these epidermal cells manufacture their own pigment or is this pigment transferred to the epidermal cells by the "dendrites" of cells derived from the neural crest and scattered at more or less regular intervals within the basal layer of the epidermis? Upon the answer to this single question rests a large share of the burden of proof, not only of the epidermogenesis as opposed to the neurogenesis of intraepidermal melanoblasts, but also of the origin of nevi and melanocarcinomas. It is stated that the epidermal melanoblasts of neural-crest origin are constant in number (Masson[15]) and that excessively pigmented skin (for example, the skin of a Negro or an irradiated person) is the result of an increased rate of formation and excretion of melanin by this constant number of "dendritic" melanoblasts. It is further assumed that the "dendrites" from each "neurogenic" melanoblast reach out and deposit the granules of melanin into the several adjacent epidermal cells, as if these latter cells functioned passively as chromatophores or melanophages.

However, the above concept of the mechanism of epidermal pigmentation appears to be rendered unacceptable by the following facts. In the first place, it has been repeatedly shown that the number of epidermal melanoblasts (i. e., dopa-positive cells) is not constant but varies with race, irradiation, and other conditions (e. g., Laidlaw,[19] Peck[20]). Moreover, in some instances, every basal cell is dendritic (Bloch[7]), and long continuous segments of the cells of the basal-cell layer may be dopa-positive. Secondly, in the pigmented epidermis of the Negro or in irradiated skin, the melanin is characteristically localized predominantly as a supranuclear cap in the admittedly obvious, truly epidermal cells. Such supranuclear orientation

of pigment suggests not passive transfer of that pigment from a "dendrite" originating several cells away, but rather, because of the polarization, its in situ manufacture. Thirdly, unlike the irregular pigment granules of melanin-filled histiocytes, the granules of pigment in the basal or prickle cells tend to be of uniform size and shape, a feature which, as indicated, is not characteristic of cells that have engulfed melanin (Pease [21]). Fourthly, when a patch of epidermis is lost, as for example, after ulceration, it is not true, as some have stated, that the capacity to form pigment is necessarily lost. On the contrary, the regenerated epidermis may be even hyperpigmented. Does this mean that cells derived from the neural crest have grown, at constantly spaced intervals, into the basal layer of the regenerating epidermis of the skin? If so, from where do such melanoblastic "neural" cells come in adults? What do they look like if they are presumed to lie dormant prior to the formation of the ulcer? Surely there is no histological evidence to indicate that, after an ulcer forms, dermal nerves or cells of Schwannian sheaths proliferate and migrate upward so as to become incorporated into the epidermis as melanoblasts. The evidence, supported also by electron microscopy (Pease [21]) is overwhelmingly in the other direction, namely, that the renewed epidermis itself forms its own melanoblasts.

The Nature of the "Dendrites" of Epidermal Melanoblasts.—Thus far, we have presented positive reasons for regarding the "dendritic" cells as modified basal epithelial cells. In addition, there are several basic reasons for specifically disbelieving that they are neural in nature.

A feature of the neurogenic theory that has been found attractive is the constant reference to the "dendrites" of melanoblasts. Dendrites are freely and easily given a neural connotation, as if their mere presence proves the neurogenesis of the appertaining cells. This assumption is extraordinary, if only for the manner in which it has speciously dominated thought on this subject.

True neural dendrites, such as occur at neuronal synapses, have basically distinctive features not present in the "dendrites" of melanoblasts. The neural dendrites, as opposed to the melanoblastic "dendrites," are an integral, ever-present part of the cell body or neuron, and are stained constantly with silver, adsorbing the granules of reduced silver so abundantly as to appear solidly black both normally and in neoplasms. Moreover, the true dendrites of neurons receive impulses through other nerve structures, the axones, and transmit those impulses through its cell body down to its own efferent axone. In the case of the so-called "dendritic" epidermal melanoblasts, all agree that the dendrites receive no axone, nor do they transmit impulses. Masson [14] has stated that he "has never noticed nervous endings in contact with the dendritic cell," although meticulous search for such contact has been repeatedly made, the lack of which is regarded by those favoring the neurogenic concept as a hiatus in their evidence. On the other hand, the proved intraepithelial or dermal nerve endings, such as taste buds, Wagner-Meissner corpuscles, and Pacinian corpuscles, all are directly connected with nerve fibers that are relatively easily demonstrable.

Furthermore, what happens to these "dendrites" in the cells of the malignant melanomas and the intradermal nevus? Even the staunchest protagonists of their neurogenesis state that at least a portion of these intradermal nevi are derived from the intraepithelially located nevus by a process of *Abtropfung* or descent into the

dermis. These intradermal cells, as mentioned, have no "dendrites." The fate of these "dendrites," both in the nevi and melanocarcinomas, seems not to have engaged the attention of those who believe in the neural origin of these tumors. Actually, as has been previously suggested, the nevus cells and the melanocarcinomatous cells are separated from the "dendrites," when originally present, while such cells are still within the epidermis, i. e., prior to their benign or malignant *Abtropfung*. This loss of "dendrites" does not suggest the behavior of neural cells.

In regard to the lack of association of "dendrites" with the cells of the intradermal nevi and melanocarcinomas, attention should be directed also toward the relationship between the inconstancy of the presence of "dendrites" in epidermal melanoblasts as well as, on occasion, the appearance of "dendrites" in nearly all basal cells. For example, as previously indicated, Bloch [7] stated that it was the dopa reaction which first showed how very frequently pigment-forming cells have this (dendritic) form and that there are cases in which practically every basal cell has dendrites. This statement of unquestioned fact by this renowned dermatologist also seems not to have been incorporated generally in discussions of this subject. Obversely, the additional relevant fact is that in some instances, epidermal melanoblasts (melanocytes) may not be "dendritic." This fact, which may be demonstrated with the dopa reaction, has been conspicuously mentioned and convincingly illustrated by Laidlaw, in 1932,[19] but it is not one that has been given its proper weight. Furthermore, some of the epidermal cells which in sections stained routinely with hematoxylin and eosin and especially with silver stains appear to have dendrites, are found on further analysis not really to possess these structures. This illusion is based on two histologic facts. One form of such simulation is produced by the presence of closely placed granules of melanin in the intercellular spaces radiating from the several sides of a melanin-containing epidermal cell and thereby appearing as dendrites. This illusion is further fostered by the coincidental fact that melanin is strongly argyrophilic, so that silver stains reinforce the impression that these aligned extracellular granules of pigment are true dendritic processes. The second basis for the illusion is the result of the characteristic shrinkage of the frequently vacuolated, scalloped cytoplasm of the epidermal melanoblast, so that bridges of cytoplasm remain adherent to the cell membrane, often without destruction or, rather, withdrawal, as yet, of all of the appertaining prickles. This phenomenon, as mentioned, may be seen in the melanoblastic or melanocytic basal or prickle cells and in cells of the junctional nevi in their early stage of formation (Fig. 3*B*). If such cells are pigmented, silver stains will cause these intracellular cytoplasmic strands to appear as dendrites. Even if they are not pigmented, a stain for dopa oxidase or tyrosinase will show these same pseudodendrites, which owe their shape to the acquired peripheral vacuolation and corresponding cytoplasmic distortion rather than to inherent dendritic structure, in the sense of neuronal dendrites. Finally, all agree that many of the epidermal melanoblasts do have radiating cytoplasmic processes or "dendrites." Such epidermal cells contain melanin that apparently provokes the cells to form pseudopods in order to help eliminate the pigment. These same pseudopods in stellate histocytes or chromatophores in the dermis or elsewhere are not called dendrites, nor are they given any such connotation. It needs to be emphasized that these "dendrites" of the epidermal melanoblasts, unlike true neuronal dendrites, do not take the silver stains if no melanin is

present. Surely such pseudopods may stain positively for dopa oxidase or tyrosinase when they possess the uninhibited enzyme—but they are still pseudopods and not in any other sense analogous to the dendrites of neurons.

Lames Foliacées.—The so-called foliated lamina (*lame foliacée*) of the intradermal nevus has long been identified with the structures of the intradermal nevus which superficially resemble Meissner's corpuscles, and by this resemblance has in considerable measure attracted and held adherents to the neurogenic theory of nevi and melanomas. It is again pointed out that the normal Meissner's corpuscle occurs in the papilla immediately beneath the epidermis of the palms, soles, and digits. The intradermal nevus, and hence the contained *lame foliacée*, on the other hand, is rarely found in these regions. Moreover, the *lame foliacée* of the intradermal or compound nevus is infrequently subepidermal, but rather tends to lie in the middermis. After all, one expects to find sebaceous gland tumors in regions where sebaceous glands normally occur, and sweat gland tumors where sweat glands are normally present. It would appear reasonable to apply this same principle to tumors involving Meissner's corpuscles and variants or homologues thereof, rather than to believe in a frequently occurring process of dysembryogenesis with such constant heterotopia. The vitalistic explanation which has been advanced, namely, that "the Meissnerian potential" is manifested in nevi in regions in which this potential had not been previously exhausted by the normal production of Meissnerian corpuscles, is not altogether convincing. After all, for one thing, normal Meissner's corpuscles are present at birth and in childhood, as well as in later life; contrariwise, the *lames foliacées* are absent in almost all nevi of childhood,[4] increasing progressively in later years as the nevi become gradually more densely collagenized. It is this progressive fibrosis about nevus cells, as previously stated,[3] which we believe represents the explanation of the *lames foliacées*. Of course, it is apparent, from what we believe to be their nature and from our published photomicrographs † that we also believe that no special stain is required for the demonstration of these "structures," and perhaps, it is also pertinent to mention, that no special stain is required, either, for the demonstration of true Meissner's corpuscles. If it were really a fact that a special stain is necessary for their identification, then we may well ask what the *lames foliacées* look like when stained with hematoxylin and eosin. The implication would seem to be that with routine stains these structures are utterly indistinguishable from adjacent portions of the nevus. We have already indicated our position on this question.

Nerves in Nevi.—Finally, the presence of what are regarded as an excessive number of nerves within intradermal nevi as opposed to their number in the normal dermis is hardly impressive evidence for the neurogenesis of nevi. It is neither surprising nor meaningful in a specific histogenetically related sense that the quantity of nerves in association with a tumor is altered. Moreover, there are no data indicating a specificity of this phenomenon for the nevi.

SUMMARY AND CONCLUSIONS

In summary, then, we have tried in this presentation to trim down to their basic unadorned core the arguments for and against the epithelial origin of nevi and melanocarcinomas. On the positive or epithelial side we have indicated not only

† References 2 and 3.

why the pigmented cells of the epidermis are merely altered epidermal cells of the basal and overlying layers—as witness the epidermis of dark-skinned persons or the epidermis made dark by ultraviolet or other forms of irradiation. We have stressed also that the inherent capacity of individual epidermal cells to become melanoblasts is a direct link in the evidence of their participation in the formation of junctional, compound, and intradermal nevi as well as melanocarcinomas. We have emphasized that there is evidence of the direct transformation of epithelial cells into nevi and melanocarcinomas. This is the kind of evidence which seems not to have been fully utilized in the evaluation of the neurogenic concept. On the other hand, it appears that much of the pivotal evidence for the neurogenesis of epidermal melanoblasts, nevi, and melanocarcinomas is based on questionable inferences drawn chiefly from: (1) the insupportable neural connotation given to the "dendrites" of epidermal melanoblasts as well as to their argyrophilia, which is dependent on the presence of melanin rather than on an intrinsic affinity of the type possessed by dendrites of neurons; (2) the evidence, notwithstanding the patent gaps, that epidermal melanoblasts are nerve endings, and (3) the untenable hypothesis that cells migrate from the neural crest to become incorporated into the epidermis or mucosa as the only source of melanoblasts. Contrariwise, by no phrase is it implied that neural-crest cells, their derivatives or their humoral products, may not influence and control pigmentation, not only of lower animals but also of man.

In addition, we have included a brief review of some of the information we have been able to extract from a clinicopathological study of 937 cases of malignant melanomas. The major conclusions from this supplementary study are as follows:

1. Fatal or metastasizing melanocarcinomas are documentable but rare occurrences in children, and the histology of such melanocarcinomas appears fairly distinctive from juvenile melanomas.

2. Juvenile melanomas, quite benign, are occasionally observed in adults in whom they may be mistaken for the malignant lesions.

3. Superficial melanocarcinomas, as herein defined, are associated with a better prognosis, as a group, than are the deep melanocarcinomas.

4. Patients with melanocarcinomas have a diathesis for the creation and activation of junctional nevi, so that it is not surprising that a significant percentage (3.6%) of patients had multiple primary malignant melanomas.

5. Epithelial hyperplasia, usually of the pseudoepitheliomatous variety, is an intrinsic part of the evolution of melanocarcinomas.

6. The prognosis in women with melanocarcinomas is appreciably better than that of men, especially with lesions of the skin of the head and neck region.

7. Melanocarcinomas of mucous membranes of the head and neck and anogenital regions bear a uniformly grave prognosis.

8. Local recurrences or metastasis to regional lymph nodes obviously aggravate the prognosis but do not preclude survival. Moreover, five-year survival is by no means tantamount to cure.

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MANAGEMENT OF PIGMENTED NEVI

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THE MANAGEMENT of pigmented nevi presents many problems. Methods of treatment and clinical attitudes differ among the surgeons, oncologists, and dermatologists. It has been realized that only by a close liaison between these specialists could the varying concepts be reconciled not only for the management of pigmented nevi but for the therapeutic approach to other tumors of the skin. With this need in mind a Visible Tumor Conference was organized at the Skin and Cancer Unit of the New York University-Bellevue Medical Center, which is attended by dermatologists, a dermatopathologist, a general pathologist, and representatives of the oncological and radiotherapeutic departments. Patients with tumors of the skin that present difficulties of diagnosis or therapy are referred for the opinion of this group, which meets once weekly. Not infrequently at these conferences pigmented nevi, with or without suspected malignancy, and malignant melanomas are seen.

HISTOLOGIC CONSIDERATIONS

Traub and Keil [1] in 1940 presented a classification of pigmented nevi based on the histologic structure of the lesions. In their classification, nevi are separated into five groups; (1) the intraepidermal nevus, (2) the intradermal nevus, (3) the junction type nevus (Satenstein *) or borderline melanoma (Becker, Sr.[2]), (4) the combination type nevus, and (5) the blue nevus. The intraepidermal type is characterized by proliferations of normal epithelial cells in the epidermis; a mixture of prickle and basal cells with or without pigment. The intradermal nevus is identified by the presence of mature nevus cells in the cutis in stands and nests. In the junction type nevus proliferation of nevus cells occurs in the epidermis, at the epidermodermal junction. The combination type presents features of the intraepidermal, intradermal, and junction types. The blue nevus is defined as a melanin-producing type of connective tissue growth. The term "pigmented" nevus, as used in this presentation, is employed with the realization that some lesions in this group may lack visible pigment but from the histologic viewpoint are properly classified in this grouping.

Traub and Keil attempted to identify the various clinical forms of nevi with the above histologic classification. In a broad sense this can be done with many nevi.

Read in the Symposium on Pigment and Pigment Tumors before the Bronx Dermatological Society, Dec. 18, 1952.

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* Satenstein, D. L., cited by Traub and Keil.[1]

Traub and Keil, however, indicate that it is difficult to correlate the clinical diagnosis with the histologic findings in all nevi. This difficulty is generally encountered by most dermatologists. It has not infrequently been my experience to find under the microscope a junction type of cytology in nevi that appeared clinically to be intraepidermic or intradermic types of lesions.

Traub and Keil,[1] Sachs, MacKee, Schwartz, and Pierson,[3] Allen,† and Becker, Sr.[7] regard the junction type of nevus as the forerunner of the malignant melanoma. On the other hand, Lund and Stobbe [8] take exception to this point of view. In the past many observers, including Unna,[9] have indicated that the pigmented nevus undergoes a tendency toward a definite pattern of developmental changes throughout life. This concept implies that, although different types of pigmented nevi can be identified and differentiated, many of these are the same process in various stages of formation. Masson [10] describes nevi in terms of a dynamic process involving a downward migration of intraepidermic melanin-forming cells joining in the dermis with Schwannian cells of nerve origin. Masson states that as long as there is migration of the melanoblasts the nevus is compound in character, and when the process is completed the lesion is then intradermic. Lund and Stobbe [8] have demonstrated that there are progressive changes in the histologic appearance of nevi throughout life. They studied nevi of various durations and noted a general trend of transitions in different age groups. Lund and Stobbe state that there is an expected incidence and degree of junctional proliferation in each age group, greatest in the first decade and diminishing in the older age groups. It is apparent that full evaluation of the significance of junctional proliferation must await further study. It would appear that the malignant melanoma is derived from the epidermal-dermal zone and may be the result of an alteration in junctional proliferation.

Although the histopathologic findings are usually helpful to the clinician, there are occasional situations in which the findings are not certain and the most competent pathologists are unable to agree among themselves as to the character of the lesion. The cytology in nevi removed from children prior to puberty is frequently misleading, as Spitz [11] has pointed out. The same occurs in nevi removed from adults where the changes may be early in development or borderline in character. The more frequent use of the serial section technique will occasionally uncover findings that the single sections or sparse sections fail to do. Occasionally the clinician does not provide the pathologist with adequate information in regard to the morphology and history of the lesion, so that the most efficient coordination is not always achieved.

REMOVAL OF PIGMENTED NEVI

General Considerations.—The patient presents his nevi to the physician for various reasons. Some patients are concerned about the presence of one or several lesions on visible portions of the body, particularly the face, because of their real or imagined unsightly appearance. Others, particularly as a result of the education of the general public in cancer detection, consult us because of nevi that they fear are malignant or may become so. If there is no clinical evidence of malignant activity, the patient can be thus informed and the nevus be left untreated. This reassurance is occasionally not enough for some patients; for them it is advisable that the lesion in question be removed as a means of calming their fears.

† References 4 to 6.

It is generally agreed that it is good practice to remove nevi that exist at sites of trauma, such as the hands and feet, bearded area of the male, and points of pressure from garments. It is most desirable to remove these lesions in children prior to puberty.

Since some of the nevi that appear after puberty do become malignant, it is considered advisable to remove new nevi that show rapid growth in the adult.

Methods of Removal.—The dermatologists have utilized the electrical and chemical destructive modalities (electrodesiccation, electrolysis, actual cautery, trichloracetic acid, carbon dioxide snow, and others) for the removal of the benign pigmented nevi for several generations. In recent years some dermatologists and most surgeons have indicated that surgical excision is the treatment of choice. Schoch [12] in 1951 conducted a survey of the methods used for treating pigmented and nonpigmented nevi by 50 dermatologists of professorial rank. Forty indicated they employ electrosurgical methods with or without curettage exclusively; seven limit removal to surgical excision; and three stated that they use both methods approximately equally. Recently, Shaw [13] received answers to a similar type of questionnaire from 201 dermatologists with an average of 20.8 years of experience. The majority varied their method of treatment from case to case, depending on their clinical evaluation of the situation. Only 7% used surgical excision in at least 90% of the nevi treated, while 70% used nonexcision methods on 90% of the lesions that they treated.

Shaw [13] attempted to evaluate how often the dermatologist erred in making a clinical diagnosis of a benign pigmented nevus; removed it by methods other than surgical excision; and later found that the original diagnosis was incorrect and the patient developed a malignant melanoma. Twenty-three dermatologists admitted 29 instances in which they made a mistake in diagnosis. From Shaw's data this is an incidence of error of 1 in 56,000. These observations appear to indicate that the well-trained dermatologist possesses the ability to diagnose and treat the benign pigmented nevi with a minimal occurrence of error.

Sachs, MacKee, Schwartz, and Pierson [3] and Traub [14] have stated that the junction type nevus requires complete excision as the only method of removal because of its premalignant character. Driver and MacVicar [15] recommend either complete scalpel excision or thorough destruction for this type of lesion. Since it is impossible to clinically identify every lesion in which epidermodermal cytology is present, it would then follow, if one accepts the concept that the junction nevus is a precancerosis, that all nevi, when removed, should be totally excised. Since there are those who deny that junctional proliferation implies premalignant potentiality, this point of view awaits future clarification.

Sulzberger and Baer [16] have stated that removal by scalpel or electrosurgical excision is advisable for pigmented nevi situated in areas where repeated trauma is present. I feel this should be particularly emphasized for nevi of the hands and feet.

The blue nevi very rarely become malignant. They are frequently seen on the extremities and are hard to distinguish clinically from the other pigmented nevi. For this reason, when they appear at sites of trauma surgical excision is advisable for these lesions.

Those physicians that recommend surgical excision and biopsy for all nevi removed must realize that the microscopist is not always able to clearly distinguish the malignant from the nonmalignant lesion (see Case Reports).

We must, therefore, conclude that each case is an individual problem, and, in the present state of our knowledge, the results obtained will depend to a large extent on the clinical judgment and experience of the individual physician.

MALIGNANT MELANOMA

Changes of pigmentation in a portion of a nevus or the entire lesion, inflammatory reaction, pain, pruritis, scaling, pyogenic or sanguinous crusting, episodes of bleeding, ulceration, regional adenopathy, and evidence of enlargement are suspicious signs of the presence of the malignant melanoma. The above may appear not only in nevi that have been present since early life but also in relatively new lesions appearing in adulthood.

It should be pointed out that the malignant melanoma may simulate many other clinical entities. The preliminary differential diagnosis frequently includes such possibilities as granuloma pyogenicum, angioma, fibroangioma, fibroma, inflamed or infected nevus, pigmented basal-cell epithelioma, hematoma, glomus tumor, Kaposi's sarcoma, seborrheic keratosis, and other entities. The requirement of microscopic examination in all situations of doubt is self-evident.

There is no question as to the proper therapy in the removal of lesions that show malignant change. Wide scalpel or electrosurgical excision is definitely indicated. The dermatologist is the specialist best able to recognize these changes, and his experience should be enlisted by other medical specialities to prevent needless mutilating surgery for benign lesions. On the other hand, it is my experience that when the dermatologist is confronted with a lesion that clinically suggests malignant activity, collaboration with the oncologist is most desirable. Our experience at our Visible Tumor Conferences further substantiates this point of view. The surgeon is at a disadvantage when he does not have the opportunity to see the primary area of malignancy in situations in which his skills are required to remove draining areas in the management of the malignant melanoma. We have consequently set up this team approach in the conference group, and I have found it equally practicable in private practice. The removal of a portion of tissue for microscopic examinations is a most helpful procedure and prevents needless extensive surgery. If malignant proliferation is found, total removal is delayed by only two, three, or four days. Most authorities (Becker Sr.[7]; Sachs, MacKee, Schwartz, and Pierson,[3] and others cited by the latter authors) agree that removal of a biopsy specimen does not in itself produce metastasis. Where the suspected lesion is small, the excision of the entire growth is more practical. If the lesion is found to be benign, a second procedure is thus avoided.

The management of the malignant melanoma lies in the province of the competent surgeon, who is best able to do a wide excision utilizing his skills in employment of skin grafts, flaps, etc., to accomplish the best type of removal of the lesion for the patient, as well as providing the surgical attention required for the draining sites.

REPORT OF CASES

CASE 1.—J. G., a white woman, aged 19, was seen in November, 1950. She presented a lesion on the right side of the chin of five months' duration. She stated that she had had a "pimple" in this area that she had attempted to express. No pus was observed, however, by the patient. There had been no preceding lesion in this site. The "pimple" failed to heal, and

a physician was consulted, who cut off the top and applied a silver nitrate solution. The lesion continued to grow. Examination revealed a 5-mm. dome-shaped, keloidal, slightly yellow growth, whose surface was covered with telangiectatic vessels.

In December, 1950, the lesion was excised and a microscopic examination was made (Figs. 1 and 2). The dermatopathologist diagnosed the lesion as "nevocarcinoma," but in his description stated the following: "I have so far found no mitosis. This is a nevo-carcinoma associated with pseudo-epitheliomatous hyperplasia or an actual prickle cell epithelioma. I am inclined to the former."

Fig. 1 (Case 1).—Lesion diagnosed as a nevocarcinoma by a dermatopathologist. Four leading general pathologists gave the following diagnoses: (1) juvenile nevus, nonmalignant; (2) potentially malignant lesion; (3) malignant melanoma? and (4) malignant melanoma. Magnification: ×150.5.

The section was then sent to four leading general pathologists. The first reported the growth as a juvenile nevus, nonmalignant in character; the second stated that the lesion should be considered as potentially malignant; the third indicated that the findings suggested a malignant melanoma, but did not feel a definite diagnosis could be made; and the fourth made a diagnosis of malignant melanoma.

Because of the inconclusive histologic findings and divergent opinions, a wider area of skin was excised. No abnormalities were found in this tissue. The patient has been seen at frequent intervals. When last seen in December, 1952, there was no recurrence or evidence of metastasis.

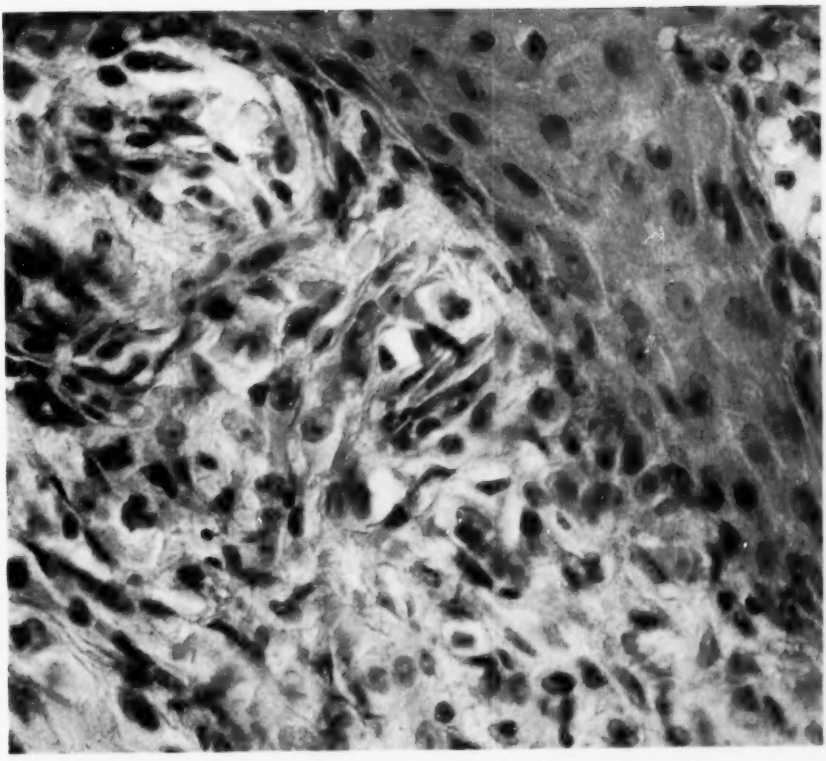

Fig. 2 (Case 1).—Same lesion as in Figure 1. Magnification: ×498.

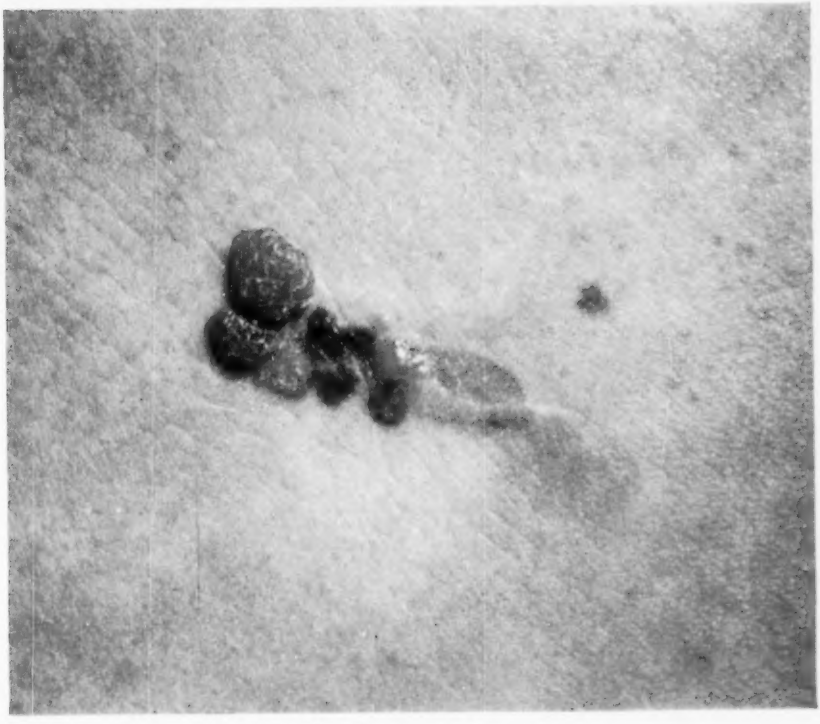

Fig. 3 (Case 2).—Appearance of recurrent nevus.

CASE 2.—M. C., a white woman, aged 45, was first seen in June, 1951. She stated that she had had a mole excised from the skin on the right side of the back 10 months previously. The patient had been aware of this lesion for three years. A microscopic examination had been made. The histologic diagnosis was "benign papillary nevus." According to the patient, five months after the excision, a recurrent lesion appeared in the scar and increased in size. This lesion, located on the right side of the back at about the level of the 12th rib, measured 3 by 1.2 cm. It was irregular in outline, with evidence of a healed scar traversing the lateral portion. The growth was raised, pink in color, with a dark brown area in the center. (Fig. 3). There were no palpable nodes in the right axilla.

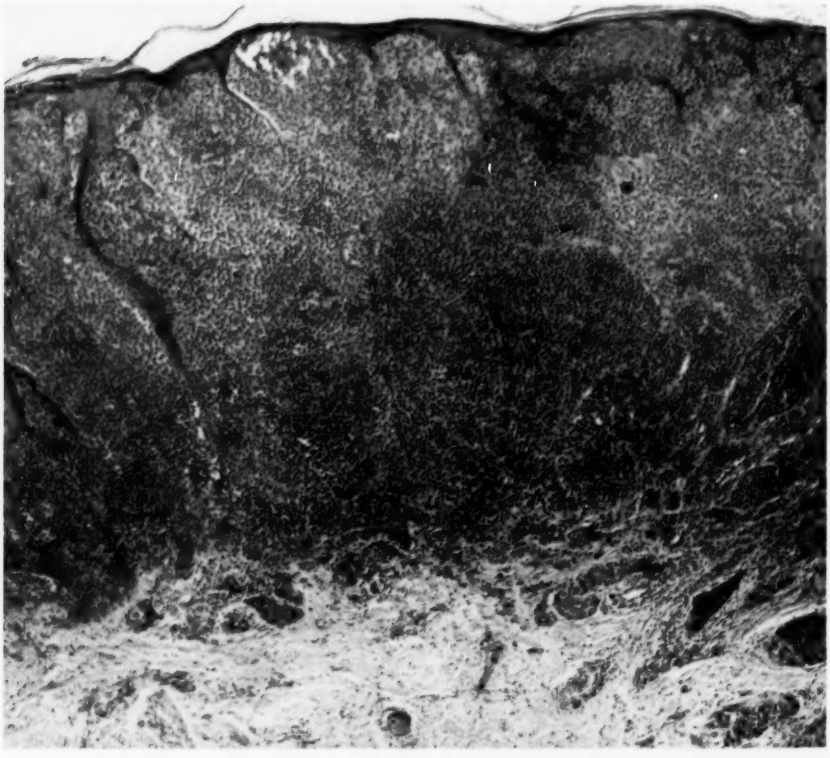

Fig. 4 (Case 2).—Lesion diagnosed as a pigmented nevus of the skin. The pathologist did not feel a diagnosis of malignant melanoma was warranted. Magnification: ×65.4.

The lesion was excised with a wide margin of normal-appearing skin. This material was presented for histologic examination. (Figs. 4 and 5). The report was "pigmented nevus of skin." The following additional note, however, was included: "The recurrent nevus is quite cellular and there is abundant evidence of mitotic activity, evidence of recent growth. There is, however, no evidence of invasive growth and the cells are not particularly pleomorphic or atypical, so that the diagnosis of (malignant) melanoma is not warranted."

The patient had two other pigmented nevi excised at the time of the removal of the recurrent nevus. One was a lesion, 3 by 2.5 cm., present for three years, located in the right scapular area. This lesion was brown, slightly raised, with an area of darker brown pigment in the center. The other nevus was removed from the dorsum of the foot. It was brown, slightly

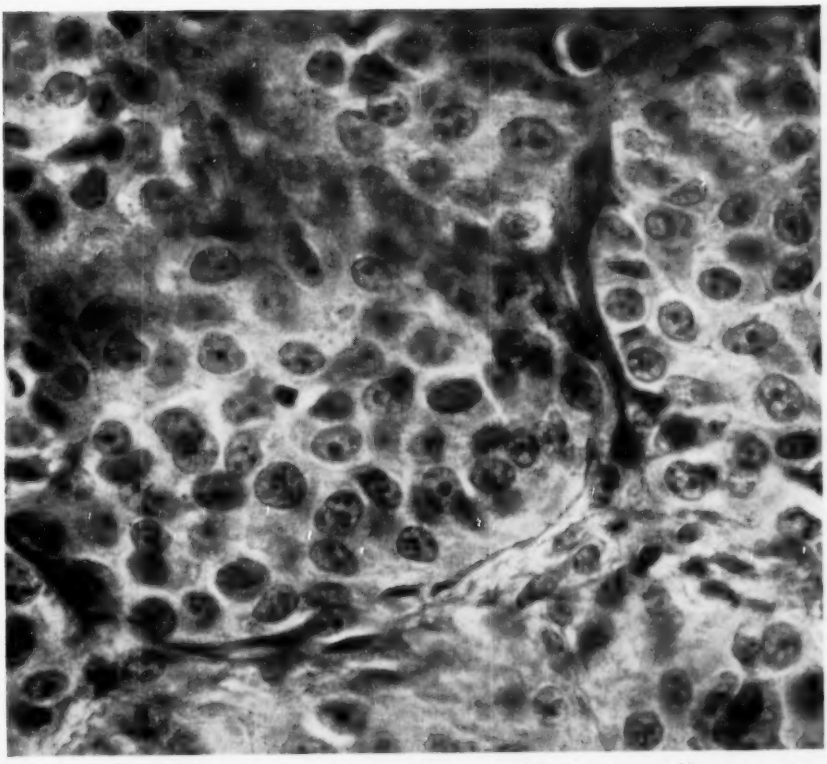

Fig. 5 (Case 2).—Same lesion as in Figure 4. Magnification: ×750.

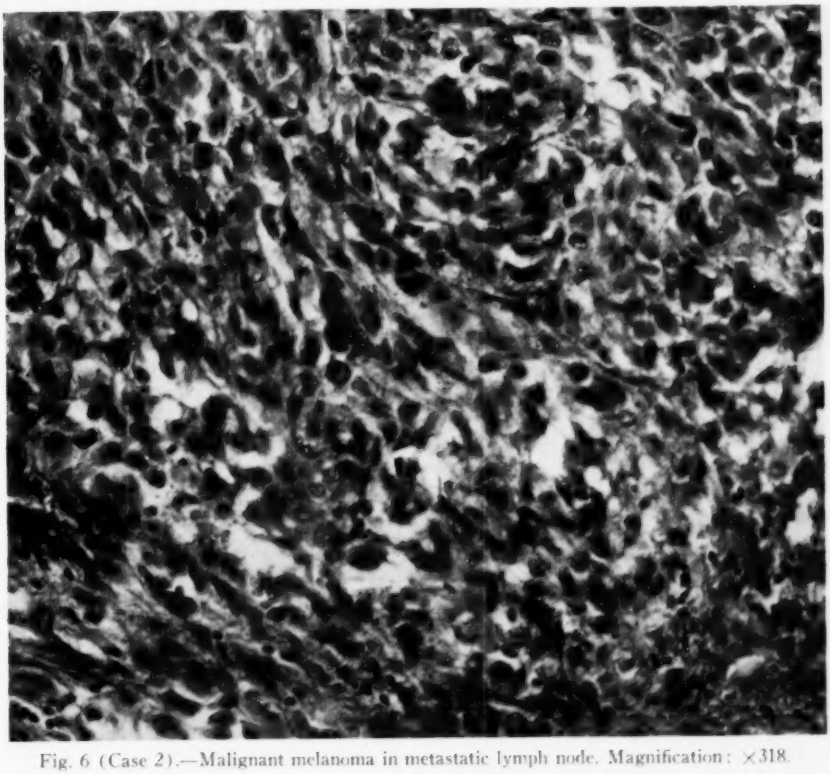

Fig. 6 (Case 2).—Malignant melanoma in metastatic lymph node. Magnification: ×318.

elevated, and had been noted by the patient for six years. The microscopic diagnosis of both of these lesions was "pigmented nevus of the skin, junction type."

In March, 1952, a pigmented nevus of the chin was also excised. This was a 2-mm. brown papillomatous lesion, elevated 4 mm. from the surface of the skin. The lesion was centered in an area of pigmented skin 1 cm. in diameter. The histologic diagnosis was "pigmented nevus."

The patient was examined periodically. On a routine follow-up examination in August, 1952, a mass, 5 to 6 cm. in diameter, was noted in the right axilla. Axillary nodes had not been palpable in previous examinations. The patient had a "lump" removed from the right breast in 1942. There has been no recurrence of this breast tumor, and the axillary mass was considered to be unrelated to the previously removed breast growth. The axillary mass was removed and revealed the presence of "secondary malignant melanoma of the axillary lymph nodes" (Fig. 6).

The axillary metastasis may have been secondary, either to the recurrent nevus of the right side of the back, or to the scapular lesion on the same side. It would appear that the recurrent nevus is the lesion that is most likely to have been the source of the metastasis. It should be emphasized, however, that whichever of these two lesions was the source, neither was diagnosed as malignant under the microscope.

COMMENT

The above case reports illustrate the physician's need for diagnostic procedures to differentiate the malignant melanoma from the benign nevus. I have seen several other cases in which this problem is presented and I am sure others have had the same experience.

The investigations of Lerner and Fitzpatrick,[17] Fitzpatrick,[18] and Becker, Jr., Fitzpatrick, and Montgomery [19] on melanogenesis may give us a method of distinguishing the malignant from the nonmalignant pigmented nevus cells of the skin.

CONCLUSIONS

There is no question about the proper handling of those pigmented nevi which show definite clinical evidence or even signs suspicious of malignant change. For those nevi which do not show such gross alterations, management for the present must depend on the features of the individual case and on the experience of the individual physician. The dermatologist is the specialist best equipped to diagnose these lesions.

We must hopefully await clinical application of further chemical, biologic, histologic, and endocrinologic studies to give us a more reliable guide in treating the pigmented nevus.

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ABSTRACT OF DISCUSSION

Dr. Marion B. Sulzberger, New York: For the past 26 years I have been sitting on the side lines listening to the pigmentary controversy. I want to call attention to one fact that is well known but that is perhaps worth emphasizing again. Regardless of the final judgment on his dopa theory, Bruno Bloch was probably the first man to carry out precise histochemical technics in histopathology, going even a little further than P. G. Unna, one of his greatest predecessors in this field.

I should like to say a few words about fundamental pigment studies of Drs. Lerner, Becker, Jr., and Fitzpatrick. It seems to me that they have carried our knowledge a good step further and have to some degree reconciled the somewhat opposite theories of Bruno Bloch and Meirowsky regarding the roles of both tyrosine and dopa.

As far as regards their clinical results with monobenzyl ether of hydroquinone, many years ago Drs. Rein, Schwarzschild, and I carried out systematic series of patch tests with this material in ointments, in solutions, and in other vehicles. Our conclusion at that time was that the bleaching effect was too irregular and too unpredictable to make this material useful clinically. Moreover, the incidence of irritation was too high to permit this chemical to be introduced for general use. The results of Lerner and Fitzpatrick's experiments are along the same lines as ours, but they have gone a step further and have once more demonstrated that with a purer chemical, the right vehicles, and the correct techniques of application there may be a real clinical place for the prescription of this material.

Concerning the excellent presentations of Drs. Allen and Spitz and Dr. Frank, if I may sum up what I got from them, it would be about as follows: It takes a great deal of microscopic experience to determine how malignant a pigmented lesion is, and also to estimate whether or not it is malignant; and it takes an even greater amount of clinical experience to estimate how malignant or potentially malignant a pigmented lesion may be when seen on the living patient. The lesion must be first evaluated clinically and a portion or the whole selected for biopsy. The question must be answered as to whether it belongs to the group of lesions which are safe to be let alone; or to those which must be removed or excised; or to those which are safe to treat by other means, like chemical destruction.

Drs. Allen and Spitz seem to reflect the views of Unna and Bloch regarding the origin of pigmented nevus cells. But since the studies of Fitzpatrick, Lerner, and particularly of S. W. Becker Jr., I was shaken in my acceptance of the idea that these cells come from the normally pigmented basal cells of the epidermis and that the Unna idea of *Abtropfung* could not be challenged. I believe now that the most convincing modern evidence supports the theory that the ordinary melanocyte comes from the neural crest and wanders into the epidermal structure.

In closing, let me give an example of a clinical evaluation by referring to myself, and telling you about two nevi of my own. One is on my right cheek, a brown, slightly elevated, hairy, pigmented nevus over which I have been shaving and which I have been traumatizing almost daily for about 43 years. It has never occurred to me to have this nevus removed. The second nevus was a little pinpoint of dark brown pigment that appeared a few months ago on the sole of my right foot. This nevus I had excised. It turned out to be one of the smallest, youngest, but most perfect specimens of a "junction nevus." I tell this personal anecdote to illustrate what I meant at first by saying that the clinician must take the lead in the recognition of those pigmented lesions which are relatively safe as compared with others which are much less safe.

DR. WILBERT SACHS, New York: The essayists of this symposium should be commended for their presentation, as well as for the thorough review of the literature. However, I find that even after the publication of our study on junction nevus-nevocarcinoma in 1947 (Sachs, W., and others: *J. A. M. A.* **135**:*216-218* [Sept. 27] 1947) there still exist differences of opinion.

Drs. Allen and Spitz have undertaken to clarify what they regard as the confused state of the problem which the late Dr. Satenstein and I have worked on for the past 25 years.

Dr. Allen spoke about tyrosine, dendritic cells, and the dopa reaction. I wish to recall the fact that Drs. Sharlit, Sims, and I reported on this subject some years ago (Histochemical Observations on Melanin Production in the Skin, ARCH. DERMAT. & SYPH. **45**:103-109 [Jan.] 1942). We were unable to produce pigment without tyrosine as well as with tyrosine. We stated that there was apparently little meaning to the dopa reaction and we questioned the existence of dendritic cells. Dr. Allen's findings seem to agree with these conclusions.

In the classification shown by Dr. Allen the intraepidermal nevus was omitted. This is a type of pigmented nevus that has no nevus cells. With respect to the blue nevus, I must stress again that, having examined many hundreds of slides, I have never seen a blue nevus become malignant. It appears to me that little is gained by substituting the term junctional nevus for junction nevus, and the same may be said for the introduction of the term combined nevus.

The nevus cells of junction nevi are present at birth or before birth. The pigment is a metabolic product of these cells. It is hardly likely that the same cells remain throughout life; they are most likely constantly replaced.

The question whether a particular lesion is a nevus or has undergone malignant change is usually determined by microscopic examination. I will agree with Dr. Sulzberger that it is at times difficult to decide; but surely, the degree of conjecture is far greater by clinical examination than by microscopic study. It is as a rule easy to make a microscopic diagnosis of junction nevus. However, it takes considerable experience, on histopathologic findings, to state whether a junction nevus has become malignant or not. When such does take place all the cells of the nevus do not change at one time, but those coming off the epidermis are the first to show the alteration and slowly push the lower and deeper ones out.

As far as junction nevi in children are concerned, I am happy to learn that Drs. Allen and Spitz do not feel that every junction nevus in children under puberty is benign. Some of them do become malignant, but not nearly as often as in adults.

I have often stated that there is no such entity as extramammary Paget's disease. I would like to emphasize that extramammary lesions are not necessarily Bowen's disease or nevocarcinoma without pigment, but may be other types of anaplastic epithelioma.

I have the courage to state that, aside from the junction nevi, all other pigmented nevi either never become malignant or do so very rarely.

In summary, a junction nevus is the only pigmented nevus that can become a nevocarcinoma, and should be removed as soon as diagnosed. When a junction nevus becomes malignant, the process is that of either an early or a late nevocarcinoma. In the early lesion, wide excision should be done and the tissue examined by peripheral biopsies to insure that none of the anaplastic cells remain. As for late nevocarcinoma, I believe that these cases are almost hopeless. There may be an occasional exception.

With regard to Dr. Frank's views of the methods of removing these lesions, I believe that it must be left to the individual experience of the operator: electrolysis, electrodissection, electrocoagulation, scalpel surgery, chemosurgery, or any combination. It does not matter which modality is employed, just so the removal is thorough.

DR. ARTHUR B. HYMAN, New York: The work of Dr. Lerner is of tremendous importance, and opens up new avenues of approach, since the old ones have only too often failed us.

Much of what Dr. Allen has expressed is in my opinion still controversial. For instance he stated that, of what he called the "superficial" type of nevocarcinoma, only a relatively small number metastasized and resulted in death. There are two possibilities: one, that the lesions were really nevocarcinoma, but were excised adequately, and second, that, though the histologic pictures of those that did not result in death exactly simulated the pictures of those that did metastasize, the former were in reality not nevocarcinomas, and would in any case not have caused death, because the histologic features which we associate with malignancy are not definitive and may be seen in benign lesions. Such a state of affairs, for instance, exists in junction nevi of the prepuberty group.

We must, therefore, agree with Dr. Sulzberger, who just pointed out that there is always a certain amount of histologic and clinical uncertainty. It is even more unfortunate that there is little parallelism between the correctness of the histologic interpretations and that of the clinical ones. With the criteria we possessed till now the histologic studies of nevi and nevocarcinomas added elements of doubt in many cases, though of course such studies have also frequently given help.

Dr. Lerner's new approach with reference to quantitative tyrosinase activity is a great and hopeful step forward in the elucidation of the problem in our search for definitive criteria between clinically and/or histologically nevocarcinoma-like junction nevi and true malignant neoplasms.

Dr. Allen still maintains that the nevus cell is of epidermal, not neuroectodermal, origin. The mass of embryologic and anatomic evidence is against this opinion, and was answered by Dr. Masson. Among other things Masson pointed out that hematoxylin and eosin staining is inadequate for this investigation; that the structures for which Masson created the term *lames foliacées* cannot be seen with hematoxylin and eosin, and therefore the other structures, which Dr. Allen (and some American dermatologists) calls *lames foliacées,* and which are seen in the deeper parts of some intradermal nevi with hematoxylin and eosin, are not *lames foliacées,* whatever their nature may be.

Multinucleate and giant nevus cells are seen in many benign nevi other than those of the prepuberty period; to call such cases delayed juvenile nevi is begging the question.

It has been suggested tonight that, in view of the fact that when malignant change occurs in a nevus it is either in a junction nevus or in the junctional elements of a compound nevus, all junction nevi should be removed prophylactically. This is, of course, in practice both impossible and unnecessary. It is impossible, because though one can, with reasonable frequency, correctly diagnose junction nevus on clinical grounds to foresee the presence of a few or some or many junction elements in most nevi, their presence can only be ascertained histologically. Such wholesale removal of all nevi which might possibly have junction elements is, of course, unnecessary, as the risk of their becoming malignant is no greater than the very risk of being alive.

DR. JULIUS H. POLLOCK, New York: It should be called to the attention of the Society that probably one of the first attempts to use clinically the monobenzyl ether of hydroquinone, with good results, was on a patient who was presented by me before the Society, and the discussion of this case appears in the ARCHIVES (ARCH. DERMAT. & SYPH. **61**:873-874 [May] 1950). I believe this antedates the appearance of Dr. Lerner's article in *The Journal of Investigative Dermatology*. The results that Dr. Lerner describes tonight coincide with the observations I then made and which at that time aroused some incredulity on the part of the members. I have continued to use the drug and continued to have similar good response in certain patients and under certain methods of application. I feel now as I did in 1949, that with this agent we probably have the best depigmentary tool that the dermatologist has in his therapeutic armamentarium to date. The very mechanism of its action makes it so.

DR. AARON BUNSEN LERNER, Portland, Ore. (by invitation): Dr. Sachs believes that enzymes play no part in normal pigmentation, because under certain conditions skin sections darken even in the presence of enzyme inhibitors. We believe that the phenomenon observed by Dr. Sachs represents pigment darkening (which is not necessarily an enzymic process) rather than new melanin formation, which normally requires the presence of the enzyme tyrosinase. For example, pigment in a light form may be deposited in the skin; and under the proper stimulus, such as ultraviolet light, the melanin may become darker. Darkening in this instance does not represent new melanin formation associated with enzymic activity but better visualization of melanin already present.

Dr. Allen takes issue with us on three points. First, he believes that melanin can be found in the nucleus of the melanocyte. Second, he does not feel that the tyrosinase reaction can ever be used to diagnose or to differentiate benign from malignant nevi. Third, he believes that the melanocyte is of epidermal and not of neural crest origin. Regarding the first two points, I should like to say that there is misunderstanding rather than disagreement. Concerning the third, there is disagreement. Our views concerning the presence or absence of melanin in the nucleus are not rigid. Detailed studies have shown that no tyrosinase is present in the nucleus, and for that reason we claim that melanin is formed not in the nucleus but in the cytoplasm. We have not said that melanin could not be deposited in the nucleus or outside the cell.

We have not stated that the tyrosinase reaction can be used to differentiate benign from malignant nevi. The tyrosinase reaction has been used in unusual cases to help one decide whether a melanoma or some other type of malignant growth is present. At times it is difficult to make the diagnosis of malignant melanoma. When cancerous tissue is incubated with tyrosine and a black pigment forms, one can be fairly certain that the tumor is a melanoma. We are investigating the possibilities of using the tyrosinase reaction to enable one to differentiate a benign from a malignant nevus.

Dr. Sulzberger mentioned that his early views on the derivation of the melanocyte from epidermal cells have changed gradually to his present one in which he feels that the cells come from the neural crest. We believe even more strongly that the melanocytes are derived from the neural crest, and we do not give much credence to other mechanisms for the following reasons. During the last 20 years all experimental work with animals has shown the melanocytes to be of neural crest origin. In addition, the melanocytes of blue nevi probably also are derived from the neural crest; and when they become malignant, they give rise to malignant melanomas, just as do other types of nevi which undergo malignant change. The only evidence to support a non-neural crest origin for the melanocyte has been obtained from looking at his-

tologic slides stained routinely. In a search of the literature, little experimental work can be found other than that involving routine staining methods as mentioned. Melanin-producing cells divide very slowly; and when they are damaged, they do not regenerate. Melanomas, which are malignant tumors derived from melanocytes, do not respond to x-ray. The melanocytes produce dopa, a substance related chemically to epinephrine and arterenol (nor-epinephrine). In all these ways the melanocytes are similar to nerve cells. Dr. Allen states that with silver stains the melanin granules become darker but that nonpigmented melanocytes themselves do not take up the silver. This view may be incorrect. Dr. Scharenberg, neural pathologist at the University of Michigan, has made some beautiful silver stains of melanocytes present in melanoma. The cells themselves when stained properly combine with silver. Dr. Scharenberg, on the basis of his experience in examining silver-stained neural tissue, is also of the opinion that these cells are of nerve origin.

I should like to comment on the excision of pigmented lesions occurring on the palms and soles. We have been carrying out a survey of pigmented lesions in approximately 2,000 college students. An effort is being made to correlate color of the skin, hair, and eyes, ability to tan, tendency to freckle, frequency of lentigo, and number of nevi. The data are on IBM cards but have not yet been studied fully. However, we can say that the incidence of pigmented lesions on the palms and soles is very high, since approximately 10% of the individuals had lesions in those areas. It would be impractical to excise all pigmented lesions of the palms and soles in all people.

I wish I could answer more exactly the question regarding the nature of perihalo nevi. We think that the melanocytes are there but are inactive. We go along with the belief that this condition represents a form of vitiligo. The melanocytes cannot be seen with routine stains, and the dopa reaction is negative. With use of special stains, as has been done with the skin of human albinos, it may be possible to see the melanocytes in the perihalo nevi.

We have not treated xeroderma pigmentosum with monobenzyl ether of hydroquinone.

DR. ARTHUR C. ALLEN, New York (by invitation): There is always a certain amount of well-known risk to be calculated whenever a general pathologist chooses to discuss cutaneous pathology before a dermatologic society.

Dr. Sulzberger has stated that the pathology of nevi and malignant melanomas has not been advanced over the past few decades. Be that as it may, at least fairly well defined histologic criteria are now available for routine application to enable the pathologist to diagnose reliably nevi and malignant melanomas. No one would think to deprecate the value of clinical wisdom, but one must permit us to question the relative capacity of the clinician "to estimate how malignant or potentially malignant a pigmented lesion may be" more accurately than a thoroughly prepared pathologist can from his histologic material. We, too, wish it were possible to eliminate or to prevent the occurrence of junctional nevi, but we hardly think that the removal of all junctional nevi, wherever they are, constitutes a practicable procedure. Hence, prophylactic removal of nevi, in our opinion, should be restricted to the feet, hands, genitalia, and probably to other sites particularly subjected to chronic irritation. Nor can we subscribe to Dr. Sachs's suggestion that what are regarded as nevi clinically are treated equally well with any modality, including electrodesiccation, carbon dioxide snow, or excision; just as it is difficult to endorse the suggestion that radiation therapy is of use in the treatment of malignant melanomas (Sachs and others: *J. A. M. A.* **135**:216-218 [Sept. 27] 1947).

Dr. Sachs and others have repeatedly stressed that notwithstanding their wealth of material, they have never seen a malignant blue nevus. We predict that the literature of the next year or so from other centers will amply confirm that, unfortunately, malignant changes in these lesions do occur.

Dr. Hyman calls attention to some difference of opinion regarding the nature of *lames foliacées*. We are grateful for Dr. Sachs's expression of agreement that the *lames foliacées* are not neurogenic and, again, we state that not only are these visible with hematoxylin and eosin stains, as our publications and our Kodachrome slides this evening would seem to have revealed, but their virtual absence in childhood nevi and their increased prominence with age, apart from their histologic features, would appear to suggest a natural aging fibrosis rather than dysembryogenesis manifesting itself increasingly with age. If the *lames foliacées* are really visible only with special stains, what after all, do such structures look like with hematoxylin and eosin

stains? Surely, it cannot be thought structures more or less the size of Meissner corpuscles would be microscopically invisible. Nor can there be any who believe that Meissner corpuscles are also invisible when stained with hematoxylin and eosin. Of course, these, too, are easily seen with this stain.

The point regarding the superficial melanocarcinomas seems to have been missed and it is important enough to be restated. It is perfectly obvious that the clinical base line or common denominator of comparison between the prognosis of the superficial and that of the deep melanocracinomas is adequate local excision. Therefore, to say that only a few of the superficial melanocarcinomas metastasized and caused death because they were all adequately excised, indicates a disregard of the tragically large number of patients whose primary melanocarcinomas are adequately excised locally, yet who subsequently die of metastases without local recurrence. Secondly, as an alternative, because 20 of the 27 patients with cutaneous superficial melanocarcinomas survived, he suggests that these lesions must have been mistakenly diagnosed. Fortunately, as you know, not all malignant melanomas cause death. Of course, a malignant melanoma is commonly a fatal disease, but to require that every malignant melanoma prove lethal before the diagnosis can be confirmed, is hardly valid. Furthermore, 3 of the 27 patients surviving the superficial melanocarcinomas, developed metastases to regional lymph nodes, thereby demonstrating their potentiality. We stated explicitly that there was no histological difference between the primary lesions that metastasized and those that did not disseminate.

Concerning Dr. Lerner's remarks, I should have preferred that I had in reality misunderstood what he stated, rather than disagreed with what he said. His declaration that neither he nor his associates states that melanin is deposited only in the cytoplasm is not reconcilable with the contrary observation which was indeed made by his associate (Fitzpatrick: ARCH. DERMAT. & SYPH. **65**:379-389 [April] 1952). As a matter of fact, however, not only is melanin commonly found within the nucleus, as Dr. Spitz and I have previously shown, but there is reason to believe it may be formed there as well as in the cytoplasm (Meirowsky and Freeman: *J. Invest. Dermat.* **16**:257-260 [April] 1951). Also, Fitzpatrick suggests (and documents by a graph and diagrams in the article mentioned above) that the tyrosine-tyrosinase reaction may have use in the differentiation of active junctional nevi from malignant melanomas by virtue of the "partially inhibited tyrosinase system" in the former and the "active tyrosinase system" in the latter. That author concluded his discussion with the statement to the effect that it is his belief that the differentiation of pigmented nevi and malignant melanomas with the tyrosinase procedures "can surpass in accuracy the interpretation of routinely prepared histologic sections." With regard to the use of the tyrosinase reaction in the differentiation of active junctional nevi from melanocarcinomas, it would appear to us that a fair analogy would be to expect that the determination of the content of acid phosphatase in a rectal polyp would be more helpful in its differentiation from a rectal carcinoma than the interpretation of routine histologic sections. Clearly, this is not the case. Moreover, there is a good deal of evidence derived from data obtained by biochemical analyses of epidermis painted with carcinogens, that many of the changes in chemical equilibrium of infiltrating carcinomas are similar to those of the carcinomas in situ. The active junctional nevus is, in essential respects, analogous to a carcinoma in situ.

The meaning of an abundantly positive tyrosine-tyrosinase reaction in frankly cancerous tissue concerns an issue quite apart from the use of this reaction in the differentiation of an active junctional from a superficial melanocarcinoma. It is self-evident—if somewhat irrelevant to our discussion—that if a given piece of tissue is known to be unequivocally cancerous, the demonstration of the tyrosine-tyrosinase reaction is "fairly certain" evidence, as Dr. Lerner says, that the cancer is a malignant melanoma. But how practical is this adaptation of the procedure in the differentiation of frank melanocarcinomas from other cancers, even assuming that there is a pathologist with the time and help available who can foretell before the paraffin sections are ready that the problem of differential histological diagnosis between melanocarcinomas and other cancers is to arise, and that, accordingly, part of the tumor is to be prepared for the tyrosinase study? As an indication of the answer to this question, it might be pointed out that the dopa reaction which, as has been generally appreciated for many years, admittedly could have been put to the same use, nevertheless has been employed for such purposes with extreme rarity. The impracticalities are of an order comparable to that concerned with serial sectioning of tissues, to which Dr. Sachs alluded. This is not to say, that the tyrosinase reaction does not merit full investigation.

In addition, it does not follow that because some cells within the epidermis contain tyrosinase and others do not, they are therefore of different origins. This does not follow any more than it does that the presence of alkaline phosphatase in some of the renal tubular cells and its absence in others, or, indeed, the presence of alkaline phosphatase in some epithelial cells and its absence in others, is indicative of different histogeneses. The repeated references to the pat phrases "experimental proof," "mass of evidence," and "demonstration by special stains" of the neurogenesis of the epidermal pigmented cells have tended to become a form of perdurable anodyne. This tendency is especially evident when such phrases are used without, at least, an attempted refutatory consideration of the opposing evidence, and of the type of questions raised in the text not only of our discussions but also of those by Willis, Bloch, Meirowsky, and Dawson, among others, and, of course, that master dermatologist, Unna. Just as an isolated example, it should be mentioned that many thoroughly objective readers of the literature have the impression that the migration of neural crest cells to the epidermis has actually been observed. We repeat that, as a matter of fact, there has been no such observation of the migration of melanoblasts (or melanocytes) from the neural crest into the epidermis, nor are even the pathways of migration known. This is not merely our own interpretation; this is the acknowledgment of the experimental lists themselves.

With regard to the statement by Dr. Lerner that there are "over 500 different silver stains," we can hardly agree with it or with his statement attributing neurogenesis to amelanotic melanocarcinomas on the basis of the presence of argyrophilic fibrils within these tumors. He goes on to document his position by stating that a neuropathologist, on the basis of a presumably unpublished study of silver stains of malignant melanomas, concluded therefrom that these tumors are neurogenic. With all proper respect to the neuropathologist in question we cannot accept the statement that silver stains of malignant melanomas constitute "experimental proof" of their neurogenesis. Even a casual familiarity with the abundance of argyrophilic fibrils in many varieties of epithelial and mesenchymal, as well as neural tumors, eliminates any neural significance based on the mere existence of such fibers. Actually, what we were referring to in our presentation was the argyrophilia of the dendrites of the epidermal melanoblasts, or, if you wish, melanocytes. We stated, that unlike the dendrites of truly neural cells, as, e.g., the dendrites of neurons, which exhibit their argyrophilia independently of the presence of melanin, the "dendrites" of the epidermal melanoblasts connote neurogenesis no more than do the denrites of pigmented histiocytes. The point is that the "dendrites" even of histiocytes may be markedly argyrophilic—if they contain melanin. It begins to look as if perhaps the neurogenic concept of nevi and malignant melanomas may perhaps be impaling itself on the points of dendrites.

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USE OF ORAL PROCAINE IN CONTROL OF PRURITUS

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THE EXPERIENCE of my colleagues and me with the use of intravenous procaine for the control of pruritus has been recorded.[1] The following report covers the results of the treatment of pruritus with procaine hydrochloride administered orally. One hundred forty-five patients, representing 23 pruritic dermatoses, were studied. Seventy-eight patients had received no previous medication, and the remaining 67 had received no relief from varied types of therapy previously administered. In the latter group were included 20 patients previously treated with intravenous injections of procaine, without relief. These will be commented upon later. For the sake of convenience, we classified these patients on a neurogenic and miscellaneous basis.

In 1950, our attention was called to the use of oral procaine by Roka and Lajtha.[2] They prescribed procaine in aqueous solution by mouth to abolish pylorospasm. In the same year, Schapiro and Sadove [3] reported a patient with status asthmaticus for whom orally administered procaine was the only medication which afforded any appreciable degree of relief. Luddecke [4] treated 10 patients with oral procaine, many of whom had an allergic background. The results were satisfactory and in some instances superior to medication previously employed. Markow and others [5] reported on the comparative effectiveness of oral procaine and Tedral* in a large group of allergic conditions. They found oral procaine to be of little value in the treatment of bronchial asthma, especially when compared with Tedral, and likewise to be of no value in the treatment of hay fever, vasomotor rhinitis, urticaria, and atopic dermatitis. Ellis [6] reported successful results in 13 patients in the relief of pain and pruritus, Balfour and Wharton [7] successfully used oral procaine to control pain and spasm in esophagitis, hiatrial hernia, and gastric and duodenal ulcer.

Procaine is the diethylamino ester of paraaminobenzoic acid and is about one-fourth as toxic as cocaine.[8] It is destroyed mainly in the liver, where it is broken down into paraaminobenzoic acid and diethylaminoethanol, which are excreted by the kidneys. An excellent discussion of the pharmacology of procaine is given by State and Wangensteen,[9] together with some theories as to its action in allergic

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* Tedral formula: theophylline 2 grains (0.12 gm.), ephedrine 3/8 grains (0.022 gm.), and phenobarbital 1/8 grains (0.007 gm.).

conditions. Procaine affects all living cells, but its main action is on the nerve fibers, where it produces an attenuation in the conduction of impulses. The theories, which have been proposed, are purely conjectural:

1. Direct action on cells. The relief of myalgia and arthalgia can be best explained by the anesthetizing action of procaine on the nerve fibers carrying pain stimuli from the muscle and joints. There is also a direct action on the endothelium of the arterioles and capillaries resulting in vasodilation.

2. Antihistaminic action. There is no proof that procaine has any antihistaminic properties.

3. Antiacetylcholine action. Some manifestations of serum sickness, particularly the spreading flare about the wheal, are probably due to the liberation of acetylcholine at the nerve-fiber endings of the terminal arterioles, and their disappearance with the injection of procaine might be due to its antiacetylcholine action.

4. Epinephrine-potentiating action. This action may help the epinephrine secreted by the body to combat various allergic manifestations.

A patient highly sensitive to procaine will develop untoward symptoms within a few moments after its use. For that reason preliminary testing with procaine is suggested in cases of suspected allergy. Many clinicians use the intranasal, sublingual, or intraconjunctival application of the drug because these tests are simple and not time-consuming. We found the intradermal injection to be satisfactory. The diagnostic value of this method, however, has been questioned by some clinicians.[10] In this study, all patients in the neurogenic group were given preliminary skin tests with 1% procaine hydrochloride intradermally, and negative responses were obtained. No patient in the miscellaneous group received a preliminary skin test. In this group a careful history was taken, and a patient whose history indicated a suspicion of sensitivity was excluded from this study.

We believe that reactions to procaine and allied drugs are commoner than recorded in the literature. When one considers the very large number of patients who daily receive these drugs without serious reactions one is inclined to conclude they are relatively safe to use. There is no doubt, however, that on rare occasions serious unexpected side-effects and even fatalities do occur. In a recent report Criep and Ribeiro[10] reviewed the literature and added three fatalities, which they stated were on an allergic basis. The conclusion reached by these authors was challenged by Davis and Bryce-Smith,[11] who stated: "From a theoretical viewpoint, it is unlikely that three fatal plus 'several other severe nonfatal' reactions would occur in one clinic in one year on an allergic basis. The incidence of true allergy to procaine is accepted as being extremely low, if in fact it occurs at all."

We were unable to find any report of fatality due to the oral administration of procaine. However, numerous reactions, mild and severe, have been reported[5] to have occurred from the oral administration. These include headache, dizziness, weakness, nervousness, nausea, drowsiness, flushing, heartburn, vomiting, tiredness, cramps, diarrhea, abdominal pain, frequency, belching, visual disturbance, and palpitation. Markow and others[5] reported that 27% of their patients experienced reactions of varying severity: headache, dizziness, nausea, and cramps. It is interesting to note that in 18% of their patients to whom placebo medication was given similar reactions of varied severity occurred. This speaks strongly for the importance of psychogenic factors in patients with allergic manifestations. In our series, 12 patients (8.2%) manifested headache, dizziness, nausea, vomiting, and drowsi-

ness. These reactions appeared on the third and fourth days, were mild in type, and were readily controlled by the withdrawal of the drug. Readministration of procaine did not cause recurrence. Eight of these reactions occurred in the neurogenic group; the remaining four, in the miscellaneous group.

The medication was prescribed in capsule form, each capsule containing 250 mg. (0.25 gm.) of powdered procaine hydrochloride and 150 mg. (0.15 gm.) of granular ascorbic acid. All the patients were treated on an ambulatory basis and were observed biweekly over the period of treatment. Topical applications were used as indicated but were free of antipruritics. The effectiveness of the therapy was based upon our clinical observations and the opinions voiced by the patients themselves. Each patient was given two capsules at once and then one capsule every third hour over a period

TABLE 1.—*Dermatoses Treated with Oral Procaine*

Diagnosis	Total	Male	Female
Urticaria	22	12	13
Pruritus ani et vulvi	9	..	9
Pruritus ani et scroti	6	6	..
Neurodermatitis (generalized)	10	3	7
Herpes zoster	10	6	4
Dyshidrosis	14	5	6
Dermatitis herpetiformis	4	4	..
Neurotic excoriations	4	1	3
Nummular eczema	2	1	1
Lichen planus (generalized)	4	3	1
Lichen simplex chronicus	9	5	4
Hyperidrosis	8	2	6
Burning tongue	4	..	4
Erythema multiforme	5	3	2
Contact dermatitis	10	7	3
Acute infectious eczematoid dermatitis	5	4	1
Psoriasis	3	2	1
Senile pruritus	4	4	..
Hodgkin's disease	2	1	1
Mycosis fungoides	2	1	1
Pityriasis rosea	3	3	..
Seborrheic eczema	2	1	1
Hypostatic dermatitis	3	..	3
Total	145	74	71

* Duration of dermatoses, two days to 21 years; age of males, 16 to 72 years; age of females, 22 to 56 years.

of two days. On the third day, six capsules were given, and then four capsules daily were continued over the period of treatment. The minimum period of treatment was four days; the maximum period was eight weeks. The majority of patients received treatment for a 7- to 14-day period. On three occasions in which pain and pruritus were severe (herpes zoster and generalized neurodermatitis) a total daily dosage of 3,000 mg. (3 gm.) was given over a period of 14 days, without untoward reactions.

In cases in which response was favorable, relief, complete or temporary, was afforded within four days. This was especially true in the urticarias due to drugs (penicillin). If no relief was forthcoming within four days, we anticipated failure, and this was borne out as the study progressed, when longer periods of medication afforded no relief. Ascorbic acid was used with the procaine because we felt from our experience with intravenous procaine that it was of some value, especially in

the patient with chronic pruritus. Other observers† found the addition of ascorbic acid did not materially add to the therapeutic effectiveness when combined with procaine.

COMMENT

The evaluation of any new drug or therapeutic method, especially in pruritic dermatoses, is fraught with many pitfalls, since there are so many factors affecting

TABLE 2.—*(Group 1) Results of Oral Procaine Therapy in Patients with Neurogenic Dermatoses*

Patients	Diagnosis	Treatment, Days	Relief		
			Complete*	No†	Temporary‡
6	Urticaria	7	0	5	1
9	Pruritus ani et vulvae	7-14	0	6	3
6	Pruritus ani et scroti	7-14	0	5	1
10	Neurodermatitis (generalized)	7-14	0	6	4
10	Herpes zoster	7	6	2	2
14	Dyshidrosis	7	5	5	4
4	Dermatitis herpetiforme	7	0	4	0
4	Neurotic excoriation	7	0	4	0
2	Nummular eczema	7-14	0	0	2
4	Lichen planus	7-10	0	2	2
9	Lichen simplex chronicus	7-10	2	2	5
8	Hyperidrosis	7-14	2	2	4
4	Burning tongue	7-14	3	1	0
90	Total		18	44	28

* Complete relief, 20%.
† No relief, 48.9%.
‡ Temporary relief, 31.1%.

TABLE 3.—*(Group 2) Results of Oral Therapy in Patients with Miscellaneous Dermatoses*

Patients	Diagnosis	Treatment, Days	Relief		
			Complete*	No†	Temporary‡
16	Urticaria (penicillin)	4-7	11	2	3
5	Erythema multiforme	4-7	1	3	1
10	Contact dermatitis	4-7	1	5	4
5	Acute infectious eczematoid dermatitis	4-7	0	4	1
3	Psoriasis	4-7	0	3	0
4	Senile pruritus	7-10	0	3	1
2	Mycosis fungoides	7-14	0	2	0
2	Hodgkin's disease	7-14	0	1	1
2	Seborrheic eczema	4-7	0	2	0
3	Pityriasis rosea	4-7	1	1	1
3	Hypostatic dermatitis	4-7	0	2	1
55	Total		14	28	13

* Complete relief, 25.4%.
† No relief, 51%.
‡ Temporary relief, 23.6%.

the pruritus which are difficult to control. Among these may be mentioned spontaneous remission, fluctuating environmental influences, and, of a greater importance in many cases, psychogenic factors. We did not study a control series as we felt we were able to evaluate our observations by comparing the effectiveness of oral procaine with other recognized therapies administered to relieve pruritus in similar cases.

† References 4 and 5.

The Tables submitted are self-explanatory. The response obtained in urticaria (penicillin) and herpes zoster was most impressive. The alleviation of symptoms in three patients with burning tongue was dramatic. These patients continued symptomless for an observation period of four months after the withdrawal of the drug. Relief in dyshidrosis was encouraging. Complete relief was recorded in two instances of hyperhidrosis during the period of medication. Recurrence followed the withdrawal of the drug. In the miscellaneous group, complete relief was obtained in 25.4%, temporary relief in 23.6%, and failure in 51%. In the neurogenic group, complete relief was afforded in 20%, temporary relief in 31.1%, and failure in 48.9%. Twenty patients previously treated unsuccessfully with intravenous procaine infusions gave the identical response to oral procaine therapy.

SUMMARY AND CONCLUSIONS

One hundred forty-five patients representing 23 pruritic dermatoses were treated with oral procaine hydrochloride-ascorbic acid for the relief of pruritus. Reactions occurred in 12 patients (8.2%) and were minor, consisting of headache, dizziness, nausea, drowsiness, and vomiting. These were readily controlled by withdrawal of the drug and did not recur upon readministration. In patients in whom response was favorable, relief was forthcoming within four days after treatment was begun. No evidence of adverse systemic effects was noted when the drug was given over long periods of time. Oral procaine therapy was found to give complete relief in 22.2% of the patients, temporary relief in 27.9%, and failure in 49.9%. Oral procaine hydrochloride-ascorbic acid medication gave most effective response in the treatment of urticaria (penicillin), herpes zoster, and burning tongue. Generally speaking, the effectiveness of orally administered procaine for the control of pruritus did not exceed that of other recognized therapies prescribed for the same purpose in similar dermatoses. Procaine can be administered orally with safety and warrants a trial when other therapy fails. Our results did not rate in merit with the enthusiastic results previously reported by other clinicians.

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ABSTRACT OF DISCUSSION

DR. MAURICE J. REUTER, Milwaukee: Renewed interest in procaine hydrochloride as a therapeutic agent in pruritic dermatological conditions and in a wide variety of diseases in which pain and spasm are prominent features has emphasized the need for further studies of this drug. Dr. Beinhauer's recent report on the intravenous use of procaine in the control of pruritus was of great value, and his report today of his experiences with the oral use of the drug is very timely.

My qualifications to discuss the oral use of procaine in the control of pruritus are practically nil. While favorable effects have been reported by some, other sources had reported to me inconsistent results and that benefits obtained by others had not been generally reproducible. These conflicting reports had consequently discouraged my use of the drug therapeutically.

Dr. Beinhauer has enumerated the several theories regarding the mode of action of procaine. The use of ascorbic acid with procaine is probably based on the fact that vitamin C diminishes procaine toxicity in experimental animals. To speculate further might be intriguing but far from helpful.

Dr. Beinhauer reports that the drug is relatively safe and that he encountered only minor reactions, readily controlled by withdrawal of the drug. There has been no report of a fatality due to oral administration. However, I feel, as he does, that there is a possibility of severer untoward reactions. Because procaine is a member of the paraamino group, notorious sensitizers, Dr. Beinhauer has been very cautious in its use. His precautions are as rigid as the ones most

of us now use when giving penicillin. Patients with suspected allergy were given a preliminary skin test. Where history indicated a suspicion of sensitivity, the patient was excluded from his study.

The favorable responses obtained by Dr. Beinhauer in the urticarial syndrome from penicillin and in herpes zoster alone make the drug a valuable addition to our therapeutic armamentarium. Its usefulness as an agent for the relief of burning tongue is certainly welcome, as is its value, although temporary, in the management of dyshidrosis. Results in other dermatoses were not impressive.

Dr. Beinhauer has given us a worth-while critical clinical appraisal of his experiences with the administration of oral procaine in a variety of pruritic dermatoses. He feels that his therapeutic response to oral procaine, except in cited instances, was not superior to or as good as other therapies given in the same dermatoses for the same purpose.

My only criticism of his work is the need for a control series. I realize, however, that controls are difficult to attain in a study such as this. Dr. Beinhauer is to be congratulated for his needed and timely study.

DR. CHARLES R. REIN, New York: Dr. Beinhauer was kind enough to send me a copy of his excellent paper, which I read with a great deal of interest. During the past year, I have treated a small series of patients with pruritic dermatoses with oral procaine hydrochloride-ascorbic acid. The material employed was furnished by the Testagar & Company, Inc., under the trade name of Ascorbaine. Each yellow-scored tablet contained 300 mg. of procaine hydrochloride and 150 mg. of ascorbic acid. The composition therefore was similar to that employed by Dr. Beinhauer, except that each of the tablets contained 50 mg. more of the procaine salt than did Dr. Beinhauer's capsules.

My patients were advised to take one tablet every three hours. Side-effects were negligible, except for slight dizziness in a few cases. Effective control of pruritus was obtained in some patients, especially in those with dermatitis venenata and urticaria due to penicillin. This form of therapy appeared to be of little value in general neurodermatitis. Although my results were not as good as those obtained by the presenter, I agree with him in that this form of medication be added to the therapeutic armamentarium for the control of pruritus.

DR. FRANK E. CORMIA, New York: I should like to say a word about this very interesting paper and also congratulate Dr. Beinhauer on his continued enthusiasm in the field of drug therapy.

Since this phase of our work on the effects of drugs on itching has been completed, I have become increasingly aware of many of the fallacies inherent in any type of related clinical investigation. I am sure that Dr. Beinhauer has taken all these into consideration, and I think he has given us a conservative estimate of the value of oral procaine for the relief of itching.

It is interesting that his figures for cure, or for great improvement, are almost parallel to mine for placebo medication. It would be interesting if he could study a few additional cases and give them first the procaine and then identical placebo medication.

I have been impressed also with the great difficulty of making tests over a period of time on patients with dermatitis, because of the natural evolution of the disease and the difference in the way it will respond as it improves. I think it is extremely difficult to draw conclusions when one is testing such patients. Again, I should like to thank Dr. Beinhauer for his very fair and fine presentation.

DR. LAWRENCE G. BEINHAUER, Pittsburgh: I wish to thank those who have discussed this paper. In answer to the question of Dr. Cormia, we purposely admitted into this study the 20 patients of the neurogenic group previously treated with intravenous procaine for the control of pruritus. We felt they would furnish us with a control, as our results with them were nil so far as relief was concerned. We were able to duplicate the same results in these patients when oral procaine was administered.

After reading the paper by Markow and his associates, we did study a series of control patients not listed in the Tables as presented today. We found, as they did, that in trying to evaluate any drug for the control of pruritus, with so many factors involved, one could often obtain good or responsive results by suggestion alone. This we did accomplish on occasions by placebo medication. Singularly, we also encountered similar untoward reactions with placebos but less frequently than they did and less frequently than we did with procaine

therapy. The more experience we have with the treatment of neurodermatitis, the more we are inclined to investigate the psychogenic factors. After the first visit and a thorough medical survey, a treatment period of one-half hour is allotted to each patient. Of this, 20 minutes is spent in discussion relative to the personal, domestic, and economic factors confronting him. The remaining 10 minutes are devoted to therapy and examination. Experience has taught us that alleviation of these factors constitutes a great help in controlling pruritus and returning the patient to his regular occupation.

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CUTANEOUS REACTIONS IN THE LYMPHOBLASTOMAS

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THE LYMPHOBLASTOMAS comprise an intriguing group of diseases of interest to workers in many fields of medicine. A major unsolved problem concerning the group is whether the members constitute clinical, pathologic, or etiologic entities, or whether they are essentially variations on the same theme. Surely among some of them there are adequate differences to determine clinical entities, but this, of course, does not mean that they are pathologic or etiologic entities; indeed, the bulk of the evidence would appear to be that they are not.*

It occurred to us that a study of certain immunological reactions in these diseases would be of interest in at least two ways. First, from the point of view of the pathogenesis of the group, if the conditions were immunologically homogeneous, it would be some evidence for their etiologic and pathogenetic relatedness. Second, from the point of view of immunology, it is known that the lymphoreticular tissues are intimately concerned with antibody production.[15] In view of the fact that in the lymphoblastomas the tissue predominantly involved is the lymphoreticular, one might anticipate that there would be some disturbance of antibody production, and indeed there is a considerable body of experimental evidence which indicates that such is the case.† We shall not discuss this literature, except to say that most of this work has consisted of exposing patients with lymphoblastomas to some presumably new antigen and subsequently determining the circulating antibody levels as compared with those for similarly exposed persons not suffering from lymphoblastomas. In general, these investigations have shown that there is an impaired ability to produce antibodies.

Our studies concerned themselves, rather, with the persistence of cutaneous reactivity to antigens to which the patient presumably had been exposed prior to the onset of the disease. We wished to answer several questions about such reactivity. Would the reactivity be preserved? Would the clinical and/or pathologic groups be immunologically homogeneous? Is there a difference in persistence between the delayed and the immediate type of allergic response? Is there

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From the Department of Dermatology and the Allergy Unit, University of Illinois College of Medicine (Dr. Rostenberg), and the Department of Dermatology, Northwestern University Medical School and Cook County Hospital (Dr. Bluefarb).

* References 1 to 14.

† References 16 to 18.

a specificity in the loss of reactivity; i. e., is there a loss of reactivity to particular antigens while reactivity to others is preserved? What does nonreactivity to an antigen toward which one was once reactive signify? What are the implications of this for the theory of positive anergy?

We hasten to state that we in nowise believe that we have completely answered any of the aforementioned questions; indeed, our work so far has barely touched upon some of them. We do think that the data we have so far amassed furnish some evidence regarding the answers to certain of them.

There has been some somewhat similar work with one member of this group, namely, Hodgkin's disease. Here the cutaneous reactivity has been primarily tested with one antigen, namely, tuberculin.‡ A very small amount of work has been done in cases of mycosis fungoides.§

PROCEDURES

The cutaneous reactivity of our patients was tested with several antigens. Originally we started with tuberculin but subsequently others were added, namely, trichophytin, oidiomycin, and histoplasmin. We also tested the patients with obligatory whealing agents, such as histamine and compound 48-80 (a condensation product of *p*-methoxyphenylethyl-methylamine and formaldehyde). Unfortunately, primarily because our ideas were not completely developed at the start of this investigation, not all the patients were tested with all the substances. For tuberculin testing, OT was used; it was usually started at a 1:5,000 concentration. If this proved to be negative, the patients were successively tested to 1:1,000, 1:100, 1:10, and full strength, although in approximately half the patients the strongest concentration used was the 1:10. In no case did we label a patient as negative to tuberculin unless he failed to react to a 1:10 dilution or to full-strength tuberculin. The oidiomycin and trichophytin used were the products sold by the Hollister-Stier Laboratories.‖ The company recommends that for the initial test dose the material as sold be diluted to 1:300. Accordingly, the initial tests were done, as a rule, with this concentration, and then the concentration was increased to 1:200, 1:100, and 1:50 if the patient had proved to be negative. If the patient was positive to the initial testing, the antigens were tested at dilutions of 1:500 and 1:1,000. Not all patients were tested with all the strengths, but a patient was not labelled as negative to trichophytin or to oidiomycin unless he failed to react to the 1:100 or to the 1:50 strength.

The histoplasmin used was furnished by Eli Lilly & Company and was used for testing in its concentrated form. It is ordinarily used in a dilution of 1:1,000. The histamine used was the histamine diphosphate and was diluted to 1:100,000 for the test purposes. Compound 48-80¶ [24] is a complex amine which is stated to have the property of liberating histamine. The majority of readings for delayed reactivity were made at 72 hours. In a very few instances the readings were done at 48 hours. The readings for immediate reactivity were done at 20 minutes. On about half the patients readings for immediate reactivity to tuberculin, trichophytin, and oidiomycin were done.

‡ References 19 to 21.

§ References 22 and 23.

‖ As most dermatologists, if they have used these antigens at all, may have obtained them from other sources, we wish to emphasize that the Hollister-Stier preparations seem to be much more reactive, especially the Monilial extract, than other preparations of these same antigens that we have used. In our experience, in routine testing, reactions with these antigens diluted several thousandfold are not at all uncommon. We do not ascribe any particular virtue or significance to this; but, in assessment of the lack of reactivity of the patients in the current series, it must be borne in mind.

¶ The drug was furnished to us through the courtesy of Burroughs Wellcome and Company, Inc.

PATIENT MATERIAL

The patients studied all had some variety of lymphoblastoma or leukemia proved by biopsies of lymph nodes or other tissues, by sternal marrow smears, or by peripheral blood cell counts. In most of the patients all three diagnostic tests had been done. The various diagnoses and the number of patients in each category are given in Table 1. Table 2 gives the amount of testing that was done with the various substances.

RESULTS

The data on our patients have been grouped in various ways, for two main reasons: First, the number of tests with a given antigen in any of the conditions

TABLE 1.—*Distribution of Patients According to Type of Lymphoblastoma or Leukemia*

	Total No. of Patients *	Average Age, Yr.	Average Duration of Disease, Mo.
Hodgkin's disease	15	39.9	29
Lymphoblastoma, lymphosarcoma, giant follicular lymphoblastoma, mycosis fungoides	7	54.3	48.8
Reticulum-cell sarcoma	7	54.5	7.7
Chronic lymphatic leukemia	9	60.9	9.1
Totals for lymphosarcoma groups	38	50.2	24.0
Acute leukemia, acute myelogenous leukemia, acute monocytic leukemia	8	45.6	7.3
Chronic myelogenous leukemia	6	48	12.5
Multiple myeloma	4	55.3	5
Totals for myelogenous group	18	48.1	8.5

* Total number of patients studied was 56.

TABLE 2.—*Number of Persons Adequately Tested with the Various Substances**

	Tuberculin		Trichophytin		Oidiomycin		Histoplasmin	Histamine	Compound 48-80
	I†	D†	I	D	I	D			
Hodgkin's disease	8	13	6	10	7	10	2	8	10
Lymphosarcoma	4	7	4	7	3	7	2	7	5
Reticulum-cell sarcoma	1	6	1	3	1	3	2	4	2
Chronic lymphatic leukemia	1	8	1	9	0	9	6	3	3
Multiple myeloma	1	4	1	2	1	2	1	1	1
Acute leukemia	..	7	..	4	..	5	4	4	2
Chronic myelogenous leukemia	1	6	1	3	1	3	1	2	2
Total	16	51	14	38	13	39	18	29	25

* By adequately tested is meant that if patient failed to react, the concentrations were increased in the case of tuberculin to 1:10 or stronger and in the cases of trichophytin and oidiomycin to 1:100 or stronger.
† I means observed for immediate reactivity; D means observed for delayed reactivity.

is small, and, second, we have attempted to answer certain of the questions previously referred to. The evidence for these answers is shown primarily in the various Tables which follow.

Table 3 lists the number of persons failing to yield reactions to the materials employed. In the case of tuberculin, a person is not included in this Table unless he failed to react to the 1:10 dilution or to the full strength. For trichophytin and oidiomycin he is not included unless he was negative to the 1:100 or the 1:10 dilution.

It is obvious that there is a general depression of reactivity to the antigens, this being more marked for the delayed variety. While there appears to be a depression of the immediate type of allergic reactivity, our conclusions regarding this should be interpreted somewhat cautiously, inasmuch as there is little information about the incidence of immediate wheal reactivity to these same antigens among the normal population. Furthermore, it is dubious that old tuberculin is the ideal form of this antigen for determining whether or not a subject has immediate wheal-type reactivity to tuberculoprotein. From Table 3 it is clear that there is no depression in reactivity to obligatory whealing agents. This is especially so when it is remembered that both histamine and Compound 48-80 were used in rather high dilutions. Consequently, we can definitely say one thing concerning immediate reactivity, that the substrate, so to speak, for the development of an immediate type of allergic reaction is unimpaired in that the patients with

TABLE 3.—*Number of Persons Failing to React to Various Agents**

	1:10 or F.S. 1:10 or F.S.*				1:100 or 1:50 1:100 or 1:50				1:100 or 1:50 1:100 or 1:50				Histoplasmin Concentrated		Histamine 1:100,000		Compound 48-80 1:250,000	
	I		D		I		D		I		D		D		I		I	
	T	0	T	0	T	0	T	0	T	0	T	0	T	0	T	0	T	0
Hodgkin's disease	8	4	14	11	5	2	11	7	7	3	11	6	2	2	10	1	11	1
Lymphosarcoma	4	1	7	5	4	2	7	5	3	1	7	4	2	2	7	1	5	1
Reticulum-cell sarcoma	1	0	6	3	1	0	3	2	1	0	3	2	2	2	4	1	2	1
Chronic lymphatic leukemia	1	1	8	2	1	0	9	4	..	..	9	2	6	6	3	..	3	..
Total for above group	14	6	35	21	11	4	30	18	11	4	30	14	12	11	24	3	21	3
Acute leukemia	..	..	7	2	..	..	4	3	..	..	5	1	4	3	4	2	2	1
Chronic myelogenous leukemia	2	1	5	3	1	0	3	1	1	0	3	0	1	1	2	..	2	..
Multiple myeloma	1	1	4	3	1	1	2	2	1	0	2	1	1	1	2	1	1	..
Total for above group	3	2	16	8	2	1	9	6	2	0	10	2	6	5	8	3	5	1
Over-all total	17	8	51	29	13	5	39	24	13	4	40	16	18	16	32	6	26	4
Percentage failing to react		47		57		38		62		31		40		89		19		15

* F. S., full-strength or undiluted 0T; I and D, immediate and delayed types of allergic reactivity, respectively; T, the total number of tests done with that substance; 0, the number of the tests that were negative.

these conditions reacted normally to histamine and to a histamine liberator. Table 3 does not reveal any significant differences among the various groups, with the possible exception of chronic lymphatic leukemia. Admittedly, these opinions may not stand up as larger samples of these conditions are studied.

We have also aggregated the results of the testing in the cases of Hodgkin's disease, lymphosarcoma, lymphoblastoma, giant follicular lymphoblastoma, reticulum-cell sarcoma, mycosis fungoides, and chronic lymphatic leukemia, believing that these are all essentially the same disease, namely, a lymphosarcoma, and have grouped the results of the testing in the cases of acute leukemia, chronic myelogenous leukemia, and multiple myeloma, not asserting that these last three are essentially the same condition, but indicating that at least they are primarily myelogenous in origin, as contrasted with the aforementioned. We were not able to observe any differences between the two groups, although one must bear in mind that the numbers in the myelogenous group are very small.

As Table 1 reveals, we calculated the average duration of the disease for the various groups. It is not contended that the figure obtained for a given case is

especially reliable, but we do not believe there will be any more unreliability with a particular condition as compared with another; consequently, we think the averages for each group are quite comparable. Our purpose in calculating this was to determine if any correlations could be made between the length of time the disease had been in existence and cutaneous reactivity. We were unable to make any such correlation.

We might also mention that the severity of the illness varied in our patients, but we do not think any group was obviously sicker than any other, except possibly the patients with the acute leukemias. The patients had received a variety of therapies, such as irradiation, nitrogen mustard, urethan, triethylene melamine, and others, but we could not make any correlation between this and reactivity.

The lack of delayed reactivity is probably better shown in Table 4, which lists the persons failing to exhibit a delayed reaction to 1:1,000 OT. It, of course, should be remembered that a 1:1,000 dilution of OT is a stronger one than is ordinarily employed for routine testing.#

TABLE 4.—*Number of Persons Failing to Give a Delayed Reaction to 1:1,000 OT*

	T*	0*	% 0		T	0	% 0
Hodgkin's disease	14	13	93	Acute leukemia	8	7	87.5
Lymphosarcoma	7	6	86	Chronic myelogenous leukemia	6	5	83
Reticulum-cell sarcoma	7	7	100	Multiple myeloma	4	3	75
Chronic lymphatic leukemia	9	4	44				
Total lymphosarcoma group	37	30	81	Total myelogenous group	18	15	83
Over-all total	55	45	82				

* T, total number of cases tested; 0, number that were negative.

Table 4 shows strikingly the high degree of nonreactivity to tuberculin in patients with these diseases. It also illustrates the immunologic homogeneity of the group, again with the possible exception of chronic lymphatic leukemia.

Turning back to Table 3, it is seen that the differences in reactivity of tuberculin, trichophytin, and oidiomycin are trivial, with oidiomycin possibly slightly more reactive. If, on further study, this should prove to be true, it might merely reflect a quality of the antigen rather than indicating a specific immunologic difference in the way these conditions react to that material. It is obvious that there are far fewer reactions to histoplasmin than to the other three antigens. We would be inclined to view this as an epidemiologic difference rather than as an indication of some unique lack of reactivity toward this substance. In the case of tuberculin, trichophytin, and oidiomycin, it is reasonable to assume that most of our patients had been exposed to the respective organisms from which these materials are derived and consequently had thereby developed a hypersensitivity to them. A failure to react then betokens an immunologic alteration, the nature of which must, however, be interpreted. In the case of histoplas-

One-tenth milliliter of a 1:1,000 OT contains approximately 0.1 mg. tuberculin. First strength P. P. D. is said to be approximately equal to 0.002 mg. tuberculin. Second strength P. P. D. is said to be approximately equal to 0.5 mg. tuberculin.

min it probably is not reasonable to assume that most of our patients had been exposed to the fungus and could thus be expected to react. A failure in this case to react probably means only that the person had never met the fungus.

We also sought to compare the immediate and the delayed type of reactivity to the same antigens. Table 5 compares the total over-all immediate and delayed

TABLE 5.—*Correspondence Between Immediate and Delayed Reactions Not Necessarily in the Same Person* *

Tuberculin						Trichophytin						Oidiomycin					
Immediate			Delayed			Immediate			Delayed			Immediate			Delayed		
T †	0 †	% †	T	0	%	T	0	%	T	0	%	T	0	%	T	0	%
17	8	47	51	29	57	13	6	46	39	24	62	13	4	31	40	16	40

* A person was not included in this Table unless he was "adequately" tested, as set forth in the footnote to Table 2.
† T, total number of tests done; 0, number of the tests that were negative; %, percentage of number tested that were negative.

TABLE 6.—*Correspondence Between Immediate and Delayed Reactions in the Same Person*

Tuberculin			Trichophytin			Oidiomycin		
T *	A *	D *	T	A	D	T	A	D
29	8	12	21	11	10	22	8	14

* T, total number of tests done; A, agreement in that both types of reaction were alike, either positive or negative; D, disagreement in that one type of reaction was positive and the other negative.

TABLE 7.—*Distribution of Persons According to Antigens Which Produced Delayed Reactions**

Negative to All Three	Negative to Tuberculin; Positive to One or Both of Others			Negative to Trichophytin; Positive to One or Both of Others			Negative to Oidiomycin; Positive to One or Both of Others		
Tb † 0	Tb 0	Tb 0	Tb 0	Tr 0	Tr 0	Tr 0	Od 0	Od 0	Od 0
Tr † 0	Tr + or	Tr + or	Tr 0	Tb + or	Tb + or	Tb 0	Tr + or	Tr + or	Tr 0
Od † 0	Od +	Od 0	Od +	Od +	Od 0	Od +	Tb +	Tb 0	Tb +
13	10			12			4		

Positive to All Three	Positive to Tuberculin Only	Positive to Trichophytin Only	Positive to Oidiomycin Only
Tb +	Tb +	Tr +	Od +
Tr +	Tr 0	Tb 0	Tb 0
Od +	Od 0	Od 0	Tr 0
8	3	0	6

* Total number of persons adequately tested, 38.
† Tb, tuberculin; Tr, trichophytin; Od, oidiomycin.

reactivity to the respective antigens, but the observations for the two types of reactivity are not necessarily on the same subjects.

Table 6 gives the correspondence between the immediate and the delayed types of reactivity in the same persons. It is quite evident from the results set forth in Tables 5 and 6 that there is no necessary correlation between the two types of reactivity to the same antigen.

Theoretically, when a person develops a delayed type of sensitivity to an antigen, presumably from contact with the living organism, he inevitably also develops

a concomitant immediate type of reactivity. Consequently, one might expect a parallelism between the two types of reactivity, assuming the test solutions are equally efficient in eliciting the two types. However, it is possible that persons retain one type of reactivity better than another, or, in theory, a disease process might selectively cause the loss of one type, as contrasted with the other. It would not appear from the results of our work that the latter hypothesis is true.

We also endeavored to answer the question as to whether there was more likely to be a loss of reactivity to one antigen while reactivity to another was preserved. Table 7 sets forth the information we gathered regarding this point. It gives it for only the delayed type of reactivity, inasmuch as we had reasonable data only on this.

It is definite from Table 7 that there is no uniformity with regard to preservation of the delayed type of reactivity. About half the subjects [21] reacted uniformly in that they reacted to all the antigens, or reacted to none of them, whereas the remaining 17 subjects reacted only to one or two of the antigens.

COMMENT

It is obvious that there is a general depression of the delayed type of allergic reactivity to antigens to which the patients had presumably previously been exposed, and hence to which assumably they were at one time sensitive. In the state of present knowledge concerning the mechanisms that underlie the development of the delayed type of allergic reaction, any discussion of the reasons for the once-sensitive person subsequently failing to yield a reaction is bound to be very speculative. There are reasons for believing that the essential change in the development of this type of sensitivity is an enzymatic adaptation to the antigen. It is believed that this enzymatic adaptation takes place in the primitive reticulum cell and is passed along to its descendents.[15] It is therefore suggested that in diseases which affect the primitive reticulum cell or its descendents (and it is reasonably well agreed that lymphoid and myeloid cells are derived from this cell) there may be an impairment in the ability to perpetuate this enzymatic adaptation or in the ability of the diseased cell to react to the antigen which originally engendered the adaptation, or, finally, the enzymatic adaptation itself could be lost. In any of these situations there would be a reduction in or an absence of the delayed type of reactivity. It is suggested that the lack of the delayed type of allergic reactivity in the neoplastic diseases which we have studied can probably be explained on such a basis.

We do not wish to pursue this theoretical discussion at any great length, but we should like to point out that there have been various theoretical reasons advanced for the lack of reactivity in the once-sensitive person. One of these was the theory of positive anergy. This theory in essence asserts that the reason for the failure to react was because the person essentially had a partial immunity to the antigen in question, so that he disposed of it so rapidly that he did not have time to react to it. The fallacies of this theory have been considered elsewhere by one of us.[25] More recently, we have adduced experimental evidence against this theory.[26] We think the present findings have an important bearing on the validity of this theory in that the cases in this group of conditions, admitted by most to be neoplastic, dis-

play the same lack of reactivity as do cases of sarcoidosis, for which disease the theory of positive anergy was originally advanced. It might be pointed out that sarcoidosis is also a disease that primarily involves the lymphoreticular apparatus, and the French (Sezary [27]) place it among the reticuloendothelioses.

SUMMARY AND CONCLUSIONS

Patients with Hodgkin's disease, lymphoblastoma, lymphosarcoma, giant follicular lymphoblastoma, mycosis fungoides, reticulum-cell sarcoma, chronic lymphatic leukemia, acute leukemia, acute myelogenous leukemia, acute monocytic leukemia, chronic myelogenous leukemia, and multiple myeloma were studied for both immediate and delayed types of reactivity to tuberculin, trichophytin, oidiomycin, and histoplasmin. They were also studied for their ability to react to obligatory whealing agents, such as histamine and Compound 48-80 (a condensation product of *p*-methoxyphenylethyl-methylamine and formaldehyde).

In general, it was found that there is a marked depression of the delayed type of allergic reactivity. There also appeared to be a depression of the immediate type of allergic reactivity, but not enough information is available regarding this type of reactivity with the antigens used to answer this point definitively.

There was no impairment in the ability to react to the obligatory whealing agents; consequently, at least part of the mechanism for the development of an immediate type of allergic reaction is present.

There was no difference in behavior between the lymphosarcoma group and the myelogenous group. There was some suggestion that cases of chronic lymphatic leukemia may behave somewhat differently, but more work would have to be done before any definite statements could be made.

No correlations could be made between immediate and delayed reactivity in the same person.

There was no uniformity in the loss of delayed type of allergic reactivity to tuberculin, trichophytin, or oidiomycin, meaning that in about an equal number of cases the reactivity to one of them was lost while it was preserved for one of the others or for both.

It is suggested that the reason for the loss of the delayed type of allergic reactivity in these cases is because of interference with the reticulum cell and/or its descendants so that it cannot develop or maintain the adaptation of the enzyme system to the antigen in question.

It is suggested that the lack of reactivity in cases of sarcoidosis is based on the same mechanism.

ABSTRACT OF DISCUSSION

Dr. Harther L. Keim, Detroit: It is exactly 30 years ago this month, at the American Medical Association meeting in Chicago, that the term cutaneous lymphoblastoma was suggested as a dermatological classification of the heterogeneous dermal responses of the true lymphadenoses.

The genetic neoplastic relationship of this group of clinical pictures was already accepted by a number of pathologists. Later, the clinicians fell in line, and at present most of the "die-hard" hematologists are willing to accept the interrelationships and clinical mutations of the varying skin manifestations of a group of conditions long held to be separate and distinct clinical entities.

And now Dr. Rostenberg and his associates come along with an ingenious and, at least as far as I know, a brand-new attempt to cement further the homogeneity of the lymphomatous diseases on the basis of certain immunological reactions. Their use of skin testing to study the immunological changes in this group of diseases appears to me to have considerable merit.

Clinical observations and experimental investigations would seem to indicate that antibody production is dependent upon the reticuloendothelial system. This system is represented in the skin by the Langerhans cells in the epidermis and cutis and by the endothelium of the papillary blood and lymph spaces. Further, since the lymphoreticular tissues are intimately concerned with antibody production and the tissue predominantly involved in these diseases is lymphoreticular, skin testing takes on added significance.

As is pointed out in the paper, all previous similar work, which is rather limited, has been done with Hodgkin's disease and with only one antigen. The authors studied a total of 56 patients with four antigens, and practically all the clinical types of the diseases of the hematopoietic system, with cutaneous manifestations, are included. The diagnosis was with biopsy, sternal marrow smears, or peripheral blood cell studies. In most of the patients all three examinations were done.

The authors set out to find the answers to six questions, but, unfortunately, the scope and originality of the work does not now permit a complete and unqualified answer to any of them. However, question two particularly intrigued me. This was, "Are the clinical and pathological groups immunologically homogeneous?" When I pressed Dr. Rostenberg for a reply to this query, he wrote me, "I think we can categorically assert that they are, with the possible exception of chronic lymphatic leukemia."

Surely, if this proves to be true, we now have another important link in the chain of evidence supporting the fundamental genetic relationships of the lymphomatous diseases. I am happy to hear that these workers plan to continue their study, for it is only reasonable to assume that they will eventually find the answers to these and many other related questions.

I am certain they will be aided in their future studies with numerous and interesting technological advances. I am thinking particularly of the new work with connective tissue and the new staining techniques and electronic microscope. These new chemical and physical methods, although formidable, offer promise of yielding the type of fundamental information that might eventually contribute to a sorely needed, better basic understanding of the allergic reactions of tissues and cells.

Dr. Samuel M. Peck, New York: I wish to thank Dr. Rostenberg and Dr. Bluefarb for a very important contribution.

Many years ago, when I had a large amount of hematologic material available, I carried out intradermal tests with various antigens, such as tuberculin, trichophytin, and venom, not for their reactivity, but to study the influence of the hemogram on the resulting histopathology. I did not have the brilliant ideas which Dr. Rostenberg and Dr. Bluefarb had.

The reason I did not publish my results was that I failed to obtain consistent reactions to these common antigenic substances. I did not have the intelligence at that time to interpret it in the way the authors of this presentation did. They have now given me the explanation. I think they have an important contribution from a very practical point of view. We often see patients with chronic persistent pruritus, which does not respond to therapy, even cortisone. Sometimes we are led to suspect that we may be dealing with a lymphoblastoma. With the findings of Dr. Rostenberg and Dr. Bluefarb in mind, I feel that in such cases in which I suspect a possible lymphoblastoma I shall further carry out a series of skin tests with common antigens. Should they fail to give skin tests, I shall begin to seek for a silent, and as yet undiagnosed, possible lymphoblastoma.

Dr. Francis W. Lynch, St. Paul: Presumably some of these patients had specific or nonspecific eruptions associated with the systemic processes. Obviously, the numbers would be small, but I wonder whether the speaker has an opinion as to any relationship between the presence or absence of cutaneous involvement, its specificity, and the changes in hypersensitivity to the various antigens.

Dr. Adolph Rostenberg Jr., Chicago: Let me answer Dr. Lynch's specific question first. As he, of course, realizes, in all the cases of mycosis fungoides, and in many of the cases of

Hodgkin's disease and the leukemias there was cutaneous involvement. When there was cutaneous involvement, biopsy was done to determine its nature. We did not make any correlations between the presence of cutaneous involvement and reactivity, but I think it is a worth-while point. If we amass more data, we shall be glad to endeavor to do that. At the moment we probably could not do so, by virtue of the small number of our cases.

I want to thank Dr. Peck and Dr. Keim for their generous comments. I am glad that Dr. Keim emphasized one point which I wanted to do, but forgot, that is, the diagnostic criteria used. As he told you, all our cases were reasonably well worked up. They all had peripheral blood cell counts, sternal marrow punctures, or biopsies of one or another tissue, and in many cases several biopsies. Indeed, in many of the cases all these procedures were carried out.

We propose to continue this work. We are doing some of the work that Dr. Peck alluded to. In the abstract, we mentioned that we have done some BCG inoculations to determine whether that affects the reactivity, and we are also studying the pathologic changes developing at the site. We are not reporting on that work at this time, as so far we have done too little. We hope to continue along these lines, and also along those suggested by both Dr. Keim and Dr. Peck. Again, let me thank you.

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EXPERIMENTAL HISTAMINE PRURITUS

III. Influence of Drugs on the Itch Threshold

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IN PREVIOUS studies * a method has been developed for the measurement of pruritus. The most satisfactory itch stimulus was found to be a freshly prepared histamine phosphate solution in a special diluent.† A quantitative technique was devised so that the end-point of subjective reactivity could be measured. This end-point of reactivity was called the itch threshold and was defined as the greatest dilution of histamine which produced a recognizable pruritus. The itch threshold was then utilized as a tool for the study of physical, environmental, and psychological factors which have been thought to influence the development and severity of itching.

An assessment of the limitations of the test was deemed advisable. Accordingly, extensive testing in control subjects was performed. It was found that the itch threshold varied greatly from person to person, with extremes of reactivity between dilutions of 1:1,000 and 1:800,000,000 and an average reactivity in the 1:100,000 range. Further variations were encountered in individual subjects when they were tested at different times during the day and night, when the temperature of the tested skin was markedly elevated or reduced, and when the subject was psychically traumatized prior to retesting. Minor changes in skin temperature during the course of clinical experiments did not appreciably affect the subjective reaction to histamine. When consecutive daily and weekly tests were performed, further variations of less degree were encountered. A comparison was made also of the itch thresholds in various parts of the body, and uniformity of reactivity was found to occur only on adjacent or contralateral areas. Finally, it was ascertained that the itch threshold remained constant in these areas during the course of acute experiments lasting up to three hours. However, even under these conditions the intensity of end-point itching, as contrasted with the itch threshold, was not uniform, and it was felt that severity of pruritus could

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* References 1 and 2.

† Special buffered saline diluent: sodium biphosphate, 0.576 gm.; sodium phosphate, 2.50 gm.; sodium chloride, 8.50 gm.; distilled water to 1,000 cc.

not be utilized except in a relative sense for definitive test procedures. In the present study, therefore, only the itch threshold has been utilized to determine the effects of various drugs on itching.

MATERIALS AND METHODS

The technique for the determination of the itch threshold has been described in previous communications.* Various methods for the production of itching were investigated, and histamine was found to be the most satisfactory stimulus in that it produced ordinarily a relatively pure form of itch. This has been found to be of especial value in control subjects in whom the complications of healing and other effects encountered in a clinical study are not present. For an evaluation of the effect of any specific drug on itching, a minimum of 20 subjects was tested in most instances. Initially, an attempt was made to divide this number into 10 normal subjects and 10 patients with dermatitis or eczema. In the latter groups, itch-threshold determinations were to be performed in the involved areas, so that a comparison could be made between the effects of a drug on itching as produced in normal and in inflamed skin. However, difficulties were immediately encountered. It was found that a sufficient number of patients with widespread dermatitis was difficult to obtain. Futhermore, improvement of their dermatoses with the lapse of time made comparisons between initial evaluations and confirmatory retesting of dubious value. An added complication was the failure of the patient to report for retesting following satisfactory control of the initial distressing symptoms. In other patients, particularly those with severe dermatitis, itching frequently was elicited from time to time by the buffered saline control injection.

In the testing of any individual drug, the initial plan was as follows: (1) preliminary determination of the itch threshold, (2) administration of drug, and (3) redetermination of the itch threshold after a suitable interval when the effect of the drug was at its peak. When the itch threshold was found to be unchanged after the administration of a drug, further testing was not performed. However, if the itch threshold was altered after adminstration, an attempt was made to duplicate the results. In many instances a final confirmation of the validity of the experiment was checked by the administration of a placebo. Initially, the plan embodied the inclusion of placebo testing for all drugs given regardless of the route of administration. This proved to be practical only when the drug had no systemic side-effects and eventually was limited to some preparations given by the oral route. Owing to the frequent neglect of both the normal subjects and the patients with dermatoses to keep their follow-up appointments, these confirmatory experiments could not be completed in all cases.

The decision was made to employ a series of representative drugs having widely diversified pharmacological effects. Five preparations were administered by topical applications. Each preparation was tested in 20 normal subjects with normal skins. The first preparation contained menthol and phenol in an emulsion type base. The second, used for purposes of contrast, was Quotane lotion, which contains menthol, camphor, Quotane (1-[β-dimethylaminoethoxy]-3-*n*-butylisoquinoline monohydrochloride), and zinc oxide. Finally, two chelating solutions were employed. These solutions are ethylenediaminetetraacetic acid preparations (EDTA).[3] The first of these contained 9% of the disodium salt; the second, 15% of the calcium disodium complex. At neutral pH, chelating solutions bind bivalent ions, such as calcium, magnesium, iron, lead, and plutonium. When so bound, these ions are for the most part chemically inert. EDTA sodium, then, will bind calcium as well as other ions, and EDTA calcium will bind ions other than calcium. A solution of sodium chloride was used as a control. It is not known whether or not calcium and other ions can be removed from the skin by the application of these agents. Furthermore, it is questionable whether ionic binding would occur in normal skin to the same extent that it might in inflamed skin.

Four antihistamine drugs were tested. These were Luvistin (1-[β (N-benzylanilino)-ethyl] pyrrolidone), P-47(1-[2-(N-benzylanilino)-ethyl] piperidine), promethazine (Phenergan; (N-[2-dimethylamino-n-propyl] phenothiazine hydrochloride), and diphenhydramine hydrochloride (Benadryl). Two vasodilators, methacholine (Mecholyl) and nicotinic acid (niacin), were employed. Nicotinamide, a nonvasodilating drug, was utilized because of the similarity of its action to that of nicotinic acid. The contrasting effect of a vasoconstricting agent was studied by the employment of epinephrine. Finally, because of their widespread use in the control of pruritus and dermatitis, the effects of calcium gluconate and cortisone were determined.

A second series of drugs having their effects on various portions of the nervous system was studied. There were three analgesic preparations, Tralgon (acetyl-p-aminophenol), acetylsalicylic acid (aspirin), and codeine. Representative sedating agents consisted of pentobarbital sodium (Nembutal), sodium bromide, and chloral hydrate. For a contrast to these drugs, caffeine and sodium benzoate U. S. P. was given. The anticonvulsant, diphenylhydantoin sodium U. S. P. (Dilantin) and the antispasmodic mephenesin (Tolserol) were also tested. An additional three drugs were chosen because of their effects on various portions of the sympathetic nervous system. These included two parasympatholytic agents, belladonna tincture, and methantheline bromide (Banthine, β-diethylaminoethyl xanthene-9-carboxylate methabromide), and benzazoline hydrochloride (Prisco'ine), a sympatholytic drug. The dosage of individual preparations, route administered, number of subjects tested, time interval between administration of test drugs, and the redetermination of the itch threshold are tabulated in the summaries of the individual experiments.

REPORT OF EXPERIMENTS

Most of the data presented in the individual Tables and the Chart are self-explanatory; alterations in reactivity to histamine remain to be explained. The last column of each Table and the Chart indicates the percentage of subjects having alteration in reactivity to histamine following the administration of the test substance. Tabulated alterations consist in elevations of the itch threshold. Elevation of the itch threshold indicates that a greater concentration of histamine is required for the production of itching. Conversely, a reduction in the itch threshold occurs when itching is produced by a greater dilution of histamine. However, it is a curious and amazing fact that of some 700 test determinations made, the itch threshold was reduced in but five instances. A partial explanation may lie in the element of suggestion inherent in the administration of any drug. This point will be discussed further when the results obtained with placebo medication are tabulated.

Initially, it was hoped that tabulation of the degree of threshold elevation might prove of significance. However, individual variations were so scattered and pronounced that these findings have been omitted.

RESULTS AND INTERPRETATION OF EXPERIMENTS

The effects of topical applications on the itch threshold are shown in Table 1. All persons tested were control subjects with normal skins. It will be noted that the percentages of threshold elevation were approximately the same with phenol-menthol ointment, Quotane lotion, and the 3% sodium chloride control solution. As will be shown later, this degree of threshold elevation probably is without significance, since the degree of elevation with oral placebo medication was 17%. It is also of interest that the Quotane lotion was no more beneficial under the conditions of this experiment than was the phenol-menthol ointment. It is not known whether or not topical application of sodium or calcium chelating solutions actually bind ions present in the skin. Should penetration of the solution occur, EDTA sodium should bind calcium and other ions in a relatively inert form. EDTA calcium,

on the other hand, might bind ions other than those of calcium. The identical percentage of threshold elevation with the two chelating solutions may be due to the binding of other ions, such as magnesium. Magnesium is thought to be concerned with enzyme action and nerve conduction.

The effects of four antihistaminic drugs and of histamine are shown in Table 2. Luvistin was tested on normal and on dermatitic skin in 13 and 7 patients respectively; P-47, in 12 and 8; promethazine, in 14 and 6, and diphenhydramine hydrochloride, in 12 and 8. The wide variation in threshold elevations with the four antihistaminics deserves special comment. It is well known that the antihistaminic drugs have multiple pharmacological effects. These effects include the

TABLE 1.—*Topical Applications*

Drug	Concentration	No. Tested	Interval Before Retesting, Min.	% with Threshold Elevation
Chelating solution				
EDTA* sodium	9%	20	30	35
EDTA* calcium	15%	20	30	35
Sodium chloride	3%	20	30	15
Phenol-menthol ointment	1% phenol, 0.5% menthol, emulsion base	20	30	20
Quotane lotion†	5% Quotane, 2% camphor, 0.1% menthol, 10% zinc oxide	20	30	20

* Ethylenediaminetetraacetic acid.
† 1-(β-dimethylaminoethoxy)-3-n-butylisoquinoline hydrochloride.

TABLE 2.—*Antihistaminics and Histamine*

Drug	Dose, Mg.	Route Given	No. Tested	Interval Before Retesting, Min.	% with Threshold Elevation
Luvistin*	100	I. M. or oral	20	60	80
P-47 antihistaminic†	100	Oral	20	60	60
Promethazine‡ (Phenergan)	12.5	Oral	20	60	45
Diphenylhydramine (benadryl)	25	I. V.	20	30	30
Histamine	1	Subcut.	20	5-10	40

* 1-[β-(α-benzylamilino)-ethyl] pyrrolidone.
† 1-(2-[N-benzyl anilino]-ethyl) piperidine.
‡ N-(2-dimethylamino-n-propyl) phenothiazine hydrochloride.

following actions: antihistaminic, sedative, analgesic, local anesthetic, anticholinergic, antimotion sickness, and fungistatic. These actions are variably present in individual antihistaminics, and ordinarily not to a parallel degree. For example, Luvistin combines its antihistaminic property with a considerable analgesic effect, while diphenhydramine hydrochloride has a more marked sedating action. The antihistaminic effect of promethazine is thought to be pronounced. P-47 combines antihistaminic and anticholinergic properties. The rather wide differences in threshold elevation with the four antihistaminic drugs, then, may be due to this variation in their actions. It should be noted that after the administration of the antihistaminic drugs threshold elevation occurred with approximately the same frequency regardless of whether the site tested was normal or inflamed skin. In 19 normal subjects and 8 patients the experiments were repeated to see whether

the initial results could be duplicated. On retesting, the threshold was elevated in 7 of 19 normals and three of eight patients. Retesting was done after placebo medication in seven subjects having threshold elevation with Luvistin, in four with promethazine, and in nine with antihistaminic P-47; the threshold was elevated once in the promethazine, once in the Luvistin, and once in the P-47 group. Surprisingly, the subcutaneous injection of 1 mg. of histamine phosphate in normal subjects was found to elevate the itch threshold in 40% of those tested. The rationale for this effect is not known; it may be concerned in part with the vasodilating effect of histamine. When retesting with histamine was done, the threshold was elevated in two or four subjects.

Table 3 illustrates the effects of the two vasodilators methacholine and nicotinic acid, nicotinamide, and a vasoconstrictor, epinephrine. The variation in effects of different amounts of methacholine is difficult to explain. It is possible that with the smaller amounts the main effect is one of mild vasodilatation. With the 10 mg. dose, however, the amount of methacholine (reaching the tested site) may be sufficient actually to augment the effect of histamine and thus diminish the per-

TABLE 3.—*Vasodilators; Nicotinamide; Vasoconstrictor*

Drug	Dose	Route Given	No. Tested	Interval Before Retesting, Min.	% with Threshold Elevation
Methacholine (Mecholyl)	1 mg.	Subcut.	10	5-10	60
	5 gm.	Subcut.	10	5-10	50
	10 mg.	Subcut.	10	5-10	10
Nicotinamide	100 mg.	Oral	20	60	55
Nicotinic acid	100 mg.	Oral	20	60	45
Epinephrine 1:1,000	0.5 to 0.6 cc.	I. M.	20	15	40

centage of threshold elevation. The vasodilator nicotinic acid elevated the threshold in 45%. However, since nicotinamide had an even more frequent beneficial effect, it is probable that the mode of action of nicotinic acid is not solely one of vasodilatation. It is possible that vasodilatation may diminish experimental histamine itch by facilitating the removal of histamine. When histamine was reinjected after the administration of epinephrine, the flares were much less pronounced. Since the histamine flare is vital for the production of itching,[2] it is probable that the vasoconstriction produced by epinephrine was responsible for its beneficial effect on the histamine threshold. Repeat testing was performed in 12 subjects, of whom 11 were normals. Elevation of threshold was produced in four of seven retested with nicotinic acid, but did not occur in the three retested with nicotinamide and the two with epinephrine. Retesting was not performed with methacholine.

The effects of three analgesic drugs on the itch threshold are shown in Table 4. Of the 22 subjects tested with acetylsalicylic acid, 12 were controls, while in 10, dermatitic sites were tested. The comparable figures for Tralgon were 13 and 7, and those for codeine, 15 and 5. With acetylsalicylic acid thresholds were elevated more frequently in normal skin, while with Tralgon and codeine the reverse was true. All analgesics tested were reasonably effective in their antipruritic action. Tralgon was exceptionally good, with elevation of the itch threshold in 70% of the subjects tested. Five out of 11 subjects retested with acetylsalicylic acid again showed elevation of the itch threshold. Of four subjects retested with Tralgon, all

had repeat threshold elevation, while of five retested with codeine the threshold was elevated in two. Placebo medication was given in nine subjects having threshold elevation following the administration of acetylsalicylic acid, in four with threshold elevation after Tralgon, and in two with threshold elevation after codeine. In the acetylsalicylic acid group the threshold was elevated once and in the Tralgon group twice; it was not elevated in the codeine group.

The results of testing with three sedating and one stimulating agent are shown in Table 5. Of the 20 subjects tested with each drug, normal skin was utilized in 17 subjects tested with pentobarbital sodium, in 16 with sodium bromide, in 13 with chloral hydrate, and in all 12 with caffeine and sodium benzoate. A rather striking increase in the percentage of thresholds elevated was shown in subjects tested with pentobarbital sodium, as compared with those in whom sodium bromide and chloral hydrate were used. This was due in part to the difference in the sedating

TABLE 4.—*Analgesics*

Drug	Dose	Route Given	No. Tested	Interval Before Retesting, Min.	% with Threshold Elevation
Tralgon*	1.3 gm.	Oral	20	60	70
Acetylsalicylic acid	1.3 gm.	Oral	22	60	54
Codeine	65 mg.	Oral	20	60	50

* Acetyl-*p*-aminophenol.

TABLE 5.—*Sedatives and Stimulant*

Drug	Dose, Gm.	Route Given	No. Tested	Interval Before Retesting, Min.	% with Threshold Elevation
Sodium pentobarbital (Nembutal)	0.1	Oral	20	60	50
Sodium bromide	1.2	Oral	20	60	15
Chloral hydrate	0.5	Oral	20	60	15
Caffeine sodium and benzoate	0.5	I. M.	12	60	42

effect with the dosage employed. Persons sedated with pentobarbital sodium became very drowsy, while no noticeable sedating effect was observed in the sodium bromide and chloral hydrate groups.

It is possible, of course, that the portion of the brain affected by the drug may have influenced the results. According to Cattell,‡ the individual action sites of sedating drugs are not well delineated at the present time. An important consideration with the bromides is that their mode of action is slowly cumulative rather than immediate; the effect following a single dose may be less pronounced. Another interesting point is that chloral hydrate has, in addition to its sedating effect, a stimulating action on the spinal cord when used in large doses. Repeat testing was performed with pentobarbital sodium in six subjects; threshold elevation occurred in two. One person was retested with chloral hydrate, but with no effect on the itch threshold. Despite the observed measurable effect of pentobarbital sodium on itching, the over-all action of heavy sedation may lead at times to severe aggravation of existing dermatitis. Such sedation, by inhibition of cerebral control,

‡ Cattell, M.: Personal communication to the authors.

is apt to result in uncontrollable and prolonged excoriations in patients with severe tension or anxiety states.

The itch threshold was elevated in 5 out of 12 subjects tested with caffeine and sodium benzoate; it was reduced in 2. Reduction of the itch threshold following the administration of this drug might be expected. The rationale for the opposite effect is obscure, although there may be a decided element of suggestion in the severe local discomfort following administration. The beneficial effects of caffeine on the itch threshold may indicate that this drug is not as harmful in itching dermatoses as is commonly believed.

Results obtained by the antispasmodic mephenesin and anticonvulsant diphenylhydantoin sodium are illustrated in Table 6. It should be emphasized that the decided beneficial effect of mephenesin was obtained after intravenous administration of 20 mg. in 50 cc. of diluent. This drug must be administered slowly and special care taken during injection, since it is somewhat irritating to the vessel wall. Furthermore, the noticeable systemic effect of the drug is immediate and of brief duration. It is probable that if a satisfactory antipruritic effect is to be obtained with mephenesin the drug should be administered by multiple daily injections. Because of its locally irritating properties, this would limit its use greatly, even

TABLE 6.—*Anticonvulsant and Antispasmodic*

Drug	Dose	Route Given	No. Tested	Interval Before Retesting, Min.	% with Threshold Elevation
Mephenesin (Tolserol)	20 mg.	I. V.	10	5-10	60
Diphenylhydantoin sodium (Dilantin)	0.1 gm.	Oral	20	60	35

in hospitalized patients. Itch threshold determinations were not made after the oral administration of mephenesin. However, a series of 15 private patients with extensive dermatitis and severe itching were treated by this method, with a daily dose ranging up to 10 gm. The effects of the drug on itching were infrequent and inconstant, and no more than might be expected with comparable placebo medication. The rationale of the beneficial effect of intravenous mephenesin on itching is obscure; it may be due to a selective action on internuncial neurons.[4] Results of therapy with diphenylhydantoin sodium were not spectacular. Of four subjects with initially elevated thresholds following its use, repeat threshold elevation was obtained in but one.

The results obtained with two parasympatholytic drugs, belladonna tincture and methantheline bromide, and with the sympatholytic agent benzazoline hydrochloride are tabulated in Table 7. Because of the potency of its action benzazoline hydrochloride was given orally and was employed only in normals. Of the subjects tested with belladonna tincture, 14 were normals, while threshold determinations were made in dermatitic areas in 6. Dermatitic sites were tested after methantheline bromide medication in four patients. The remaining 16 were normals. As will be seen, benzazoline hydrochloride had a decidedly more beneficial effect than did belladonna tincture or methantheline bromide. It is possible that the threshold would have been even more favorably influenced had the drug been given by the intravenous route. However, the limitations of such a procedure, particularly in older subjects, would preclude its employment in this fashion. Furthermore, earlier clinical trials with another sympatholytic agent Dibenamine (*N*, *N*-dibenzyl-β-

chloroethylamine) resulted in marked aggravation of dermatitis. The itch threshold was reduced in one subject after the administration of benzazoline hydrochloride. It should be noted that belladonna tincture and methantheline bromide were no more efficacious than oral placebo medication. Retesting was performed in three persons given belladonna tincture and in one given methantheline bromide. Elevation of the itch threshold occurred in two of the former group and in the single case in the latter group.

In some respects the miscellaneous group, shown in Table 8, was the most interesting of all. In the first place, the fact that the itch threshold was elevated in 17% of the large group of subjects (35) tested with placebos indicates that almost any therapeutic maneuver may be helpful in the control of itching. Furthermore, it is probable that the suggestive effect of such medication may vary from day to day in individual patients. This response may be conditioned by their mood, degree

TABLE 7.—*Parasympatholytic and Sympatholytic Drugs*

Drug	Dose	Route Given	No. Tested	Interval Before Retesting, Min.	% with Threshold Elevation
Benzazoline hydrochloride (Priscoline).....	50 mg.	Oral	10	60	50
Belladonna tincture	0.6 cc.	Oral	20	60	20
Methantheline bromide (Banthine*).....	100 mg.	Oral	20	60	15

* Betadiethylaminoethyl xanthene-9-carboxylate methobromide.

TABLE 8.—*Miscellaneous Group*

Drug	Dose	Route Given	No. Tested	Interval Before Retesting, Min.	% with Threshold Elevation
Placebos	.....	Oral	35	60	17
Cortisone	100 mg.	I. M.	15	60	6
Calcium gluconate	10 cc. of 10% solution	I. V.	20	30	5

of alertness or irritability, the presence of tension or anxiety states, and their receptiveness to suggestion at that particular time. Variations encountered on retesting with various drugs may be due in part to these circumstances. In fact, differences in the suggestive element may impair the validity of the initial testing to a certain extent. It may be true also that the element of suggestion is more pronounced when the drug administered produces decided clinical side-effects.

The results obtained with calcium gluconate medication are of special interest in view of its widespread clinical use for the control of dermatitis and itching. This drug was utilized in 12 normal subjects, while the itch threshold determinations were made in dermatitic areas in 8 patients. Elevation of itch threshold occurred in only 5% of this series. It may be significant that with the particular drug employed, only 2 of the 20 subjects tested experienced any sensation of heat; therefore, the element of suggestion would be limited only to the procedure of venipuncture.

Table 8 illustrates also that a single intramuscular injection of 100 mg. of cortisone has little, if any, effect on the itch threshold. Cortisone was administered over a period of time to the 15 patients referred to, and to another 5 patients without

SUMMARY OF EFFECTS OF DRUGS ON ITCHING

Drug	Number of Subjects Tested	Percentage of Thresholds Elevated
Luvistin	20	
Tralgon	20	
Antihistamine (P-47)	20	
Mephenesin (i.v.)	10	
Methacholine(1 mg.)	10	
Acetylsalicylic acid	22	
Nicotinamide	20	
Benzazoline	10	
Codeine	20	
Pentobarbital	20	
Methacholine(5 mg.)	10	
Promethazine	20	
Nicotinic acid	20	
Caffeine (i.m.)	12	
Epinephrine	20	
Histamine	20	
E.D.T.A. sodium (topical)	20	
E.D.T.A. calcium (topical)	20	
Diphenylhydantoin	20	
Diphenhydramine (i.v.)	20	
Belladonna (tincture)	20	
Quotane lotion	20	
Phenol-menthol ointment	20	
Placebos	35	
Sodium bromide	20	
Methantheline	20	
Saline control (topical)	20	
Chloral hydrate	20	
Methacholine(10 mg.)	10	
Cortisone	15	
Calcium gluconate	20	

skin disease. In all, 20 patients were available for repeated determinations of the itch threshold during courses of oral cortisone therapy continued up to one month or more. Fourteen of this group had a severely pruritic dermatitis, which in each instance was extensive, chronic, and resistant to various types of conventional therapy. The initial dose of cortisone varied from 100 to 200 mg. daily. After three days, gradual reduction of dosage in the group with dermatitis was instituted. Dosage levels after the third week varied from 25 to 75 mg. of cortisone per day. Of the six patients without dermatitis, moderate to marked variation in the itch threshold occurred on retesting. The itch threshold was not elevated in any of these six patients after prolonged cortisone therapy. In the group with dermatitis, cortisone exerted a variable effect on the itch threshold and on the degree of clinical pruritus, but it was uniformly successful in the amelioration of the severity of the inflammatory process. Marked improvement of dermatitis coincided frequently with unabated itching. An attempt was made to correlate the improvement in pruritus with elevation of the itch threshold. When the pruritus was improved after cortisone therapy, subsequent threshold determinations revealed elevation of threshold in three, unchanged threshold in one, and reduction of threshold in four. When the degree of pruritus was not improved, the itch threshold was always reduced on subsequent examinations. This experiment would indicate that cortisone has no direct effect on pruritus and no pronounced beneficial effect on the itch threshold.

The over-all effects of all drugs and preparations tested are summarized in the Chart.

GENERAL COMMENT

A survey of the Chart demonstrates that a wide range of pharmacological preparations exert a demonstrable effect on pruritus as induced experimentally by histamine. As can be seen, these effects are secured by divergent pharmacological actions. Itching may be affected by amelioration of inflammation, local action on cutaneous cells, nerve endings, or blood vessels, and by blocking of histamine or partial neutralization of its actions. It may be influenced also by metabolic or other interference with nerve conduction, regulation of the internuncial neuron system at the spinal cord level of the itch pathway,[4] depression of synaptic transmission of impulses through sympathetic ganglia (pentobarbital sodium),[5] and alterations in interpretation at the cortical level. Further effects may be produced by drugs having primarily sympatholytic actions; the mode of their specific influence on itching has not been determined. The cortical interpretation of itching may be altered by drugs which depress cerebral excitability by their sedating action, and by placebos. The precise mode of action of placebo medications on the central nervous system is unknown.

The question arises as to the applicability of the present experiments to the clinical management of itching. It is possible that itching produced by mechanical or electrical means might be more comparable to clinical pruritus than that resulting from the injection of histamine. It would seem that itching is not solely the result of histamine liberation, but may depend also on other types of local tissue injury. Unfortunately, a satisfactory measurable itch has not been elicited by mechanical or electrical stimuli. Other drugs producing itching on intradermal injection are subject to the same criticisms as is histamine; moreover, they may liberate histamine secondarily (acetylcholine in the so-called cholinergic urticaria).

It is possible that the local effect of a drug on histamine-induced itch may not be identical to its effect on "essential" pruritus or on the pruritus associated with various types of inflammatory skin disease. Once pruritus has been initiated, however, it tends to continue for a period of time; testing during this interval cannot fail to yield significant data. In addition, when histamine is injected into inflamed and formerly pruritic skin, the resultant itching is a product not only of histamine action, but also of the preexisting dermatitis and itching.

SUMMARY

The itch threshold was utilized to study the effects of drugs on an experimentally produced itch.

Various types of preparations were studied. These included topically applied drugs with possible antipruritic and other effects, antihistaminics and histamine, vasodilators and nicotinamide, a vasoconstrictor, analgesics, sedatives, a stimulant, drugs affecting the sympathetic nervous system, calcium gluconate, cortisone, placebos, and a topically applied saline control.

Elevation of the itch threshold following the administration of a drug was the criterion for beneficial effects.

An antihistamine with analgesic effects (Luvistin [1-(β-[N-benzylanilino]-ethyl) pyrrolidone]) and an analgesic drug (Tralgon [acetyl-p-aminophenol]) proved to be most beneficial in their effect on histamine-induced pruritus. An antihistaminic drug with a conjoint anticholinergic action (P-47 [1-(2-[N-benzylanilino]-ethyl) piperidine]) had high antipruritic powers.

Antihistamine preparations varied widely in their antipruritic activity.

Moderate vasodilatation was of some apparent value in the control of itching; this effect was noted with small amounts of methacholine (Mecholyl), with nicotinic acid (niacin), and with histamine. Nicotinamide, which does not produce vasodilatation, was slightly superior to nicotinic acid.

A vasoconstrictor agent, epinephrine, had a favorable effect on the itch threshold, possibly by partial inhibition of the histamine flare.

The analgesics acetylsalicylic acid (aspirin) and codeine had a better than average effect on experimental pruritus.

The effect of sedation was moderately beneficial; it was noted mainly with sodium pentobarbital (Nembutal). Similar benefit was noted with caffeine.

Mephenesin (Tolserol) favorably influenced the itch threshold when administered intravenously; a selective effect on internuncial neurons is postulated.

Benzazoline hydrochloride (Priscoline) may temporarily diminish itching in controls, but the effect of a comparable sympatholytic agent in patients with dermatitis may be the reverse.

Cortisone had but little measurable effect on itching.

Calcium gluconate had a negligible effect on the itch threshold.

Two local ant pruritic preparations in common use had little, if any, measurable effect on experimentally produced itching.

Topical application of chelating agents having ion-binding properties favorably influenced the itch threshold in a significant number of instances.

A considerable element of suggestion is inherent in the administration of any drug for the control of itching.

ABSTRACT OF DISCUSSION

DR. BEATRICE M. KESTEN, New York: We are grateful for Dr. Cormia's continuing attack on the devilish problem of itching. My discussion will be, traditionally perhaps, the hoop-skirt one—that of covering the subject without really touching anything.

In experimental work one variable would be sufficient. Dr. Cormia has had to wrestle with at least three: the histamine response, the patient, and the individual variations in pharmacological responses to drugs.

He has effectively controlled the histamine response by determining, at the outset of the experiment, the itch threshold for each patient. All are so well aware of the inability to control emotional states, conditioning influences of past experience, and degrees of attention while testing patients.

In exploring the effect of 27 drugs on itching induced by histamine on groups of 10 to 20 patients, Dr. Cormia was confronted with many problems. To name a few, the enormity of time consumed in testing each patient precluded a larger series; the route of administration of some drugs might have introduced situational stress and modified the itch threshold; the time peak of pharmacological action of some drugs used is, I think, not known; the effects of drugs having similar pharmacological action may not have been comparable because of the dose given and the time of retesting; the vehicle is of importance in a comparison of topical applications.

Although the influence of drugs reported here on histamine-induced itching is at times at variance with our clinical experience, histamine is at present the drug of choice in the stimulation of experimental itching.

Dr. Cormia's interest was not only in drugs elevating the threshold of itching but also in the site of the drug's action. With the exception of cortisone, almost all drugs, as well as the placebo, elevated the threshold of itching in normal persons. It would seem that the groups of drugs having either antihistaminic or analgesic action, when administered orally, were the most effective antipruritics. The finding that the average dose of methacholine was well below that of the placebo in raising the itching threshold is consonant with acetylcholine being the chemical mediator in the flare which produces itching. It does not seem possible to correlate the site of action of a drug with its influence on histamine-induced itching. Drugs thought to compete with histamine at the cellular level, such as the antihistaminics, drugs which depress pain centers in the cerebrum, such as the analgesic group, nonvasodilators, such as nicotinamide, a sympatholytic drug and a vasodilator, such as benzazoline hydrochloride, and sodium pentobarbital, which produces sedation with little analgesia, were effective in raising the itching threshold in about half the patients tested.

The study of itching or pain, with its physiochemical, as well as perceptual, component, is fraught with obstacles. Now that physiologic experimentation is possible with isolated surviving dog skin and also with tissue cultures of human epidermis, fascinating methods have become available for the study of basic factors underlying Dr. Cormia's contribution. After this, it may well be possible to correlate the effects of antipruritics by testing persons who have had intensive training in sensory discrimination, with fewer variables.

DR. WALTER B. SHELLEY, Philadelphia: Dr. Cormia's work commands my admiration and appreciation. This is a magnificent body of data that we can add to our information about the basic physiology of drugs. So far as I know, it is the first controlled study on the effect of various pharmacological agents on an experimentally induced pruritus. I believe it was Lord Kelvin who said we have no knowledge without measurement. Certainly, here, Dr. Cormia has brought mensuration into the difficult subject of pruritus.

Pruritus is an extremely involved problem, as Dr. Kesten has so well pointed out. Any study or any basic experimental data cannot be rapidly translated into clinical law; but I do see in Dr. Cormia's data two clinical points. One is the fact that this method enables us to assess rapidly, in man, the new antipruritics which are appearing from time to time; and, secondly, it gives us an opportunity as clinicians to determine actually what is happening in the patients we are treating.

To be more specific, if we have a drug such as cortisone, which has a definite antipruritic effect, and we use Dr. Cormia's data as a guide or as a reference point, we see that the cortisone

probably is not acting directly in a symptomatic fashion. It is not a primary antipruritic. It more likely would appear to be acting at a cellular level, in restoring normal health and integrity to the skin and thereby eliminating pruritus.

DR. FRANK E. CORMIA, New York: I should like to thank Dr. Kesten and Dr. Shelley for their interesting and thoughtful comments.

Dr. Kesten has raised several questions regarding the presence of variables as possible sources of error. Most of these have been eliminated. There are two possible sources of error in testing involved skin of patients with dermatitis. The first is the expected difference in response as the dermatitis improves with time and treatment. Tests performed with different drugs at intervals of several days might not be strictly comparable; i. e., the drug effect would be more pronounced as the dermatitis and its attendant pruritus improved. Secondly, these patients were not especially trained in what Dr. Kesten has termed tactile discrimination. However, one person frequently was tested with several drugs. Moreover, only reasonably alert and intelligent patients were tested. Finally, they were required to decide only one thing: Was there, or was there not, an itching sensation at a specific injection site? Medical students, who comprised more than 60% of the material, were the normal subjects tested. A relatively small group of students were chosen by careful screening and were well trained in sensory discrimation. For this group, then, Dr. Kesten's criticism would not apply. Regarding the variables inherent in the injection of histamine, these have been eliminated in a previous study [2] and need not be considered.

With regard to Dr. Kesten's remark about acetylcholine, it probably is important as a mediator of flare, but it is interesting that under the conditions of our experiments, methantheline bromide had no effect upon the degree of itching. It was no better than the control placebos. Furthermore, methacholine in small doses actually raised the itch threshold to histamine in the present experiments.

I did not have a chance to discuss cortisone when I presented the paper, but not only did we make the one-hour test with cortisone, but also we followed a group of patients with severe intractable dermatitis for at least a month, with itch threshold determinations at intervals of three to four days through this entire period. A control group of five paients who were receiving cortisone or corticotropin (ACTH) for another purpose than any severe skin disease were similarly studied. We found that, even while the dermatitis was improving with corticotropin therapy, there was no constant effect on clinical itching or on the itch threshold.

Of course, these patients were selected, perhaps, in the sense that they all had severe chronic treatment-resistant dermatitis. They would probably fall into the so-called disease-prone group, of which we shall be hearing more in the next few years. Nevertheless, it was a striking thing that even when the itch threshold was elevated, there was no constancy in the improvement of the patients' symptoms. However, when there had been no improvement in itching, the itch threshold uniformly was reduced.

Dr. Shelley has summarized effectively the purpose of this work. In a word, it is to serve as a base line for the investigation of comparable drugs or of new preparations. It gives a point of reference which I hope will be of some value.

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INFANTILE CAVERNOUS HEMANGIOMAS

Persistence into Adulthood of Untreated Lesions

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A CERTAIN percentage of infantile cavernous hemangiomas, if untreated, persist into adulthood. Since they respond well to irradiation during infancy and since later they may become very troublesome, I believe the physician should advise early treatment. Since the purpose of this paper is to show that persistence of hemangiomas is not uncommon and since types of therapy are adequately covered elsewhere in the literature, only indirect reference to therapy will be made. Furthermore, various types of vascular nevi will require varying forms of therapy.

REVIEW OF LITERATURE

Whether to treat or not to treat cavernous hemangiomas is a provocative subject. A thorough review of the literature only serves to point up the lack of harmony of concepts in types of therapy, the age at which treatment should be started, or whether hemangiomas should be treated at all.

Lister,[1] who obviously included cavernous hemangiomas under the classification strawberry nevi, stated that hemangiomas "grow more or less rapidly during the first few months of the child's life, and thereafter invariably retrogress and disappear completely, leaving little or no trace on the average, about the fifth year of the child's life." His detailed review of the literature failed to disclose a single case in which the lesion failed to retrogress; consequently, he advises no treatment.

On the other hand, Rosh[2] deplores advising parents not to have hemangiomas treated, since lesions which retrogress are "rare instances. . . . In most cases, the hemangiomata usually increase in size with the growth of the child." Costello[3] cited Watson and McCarthy as stating that 73% of their patients presented evidence of hemangioma at birth and more than 85% during the first year of life. "Cavernous hemangiomas rarely disappear spontaneously," he concluded. He stated further that success of treatment depends on starting treatment in the first month of life.

Pendergrass and his associates[4] believe that a physician has no right to deny treatment to a patient because of the hope that the lesion will disappear without treatment. Ronchese[5] thinks that "the percentage of hemangiomas noted in the adult is far from small. . . . There is no reason to let the parents suffer while wait-

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Forty-five photographs were used in the original presentation, but, owing to lack of space, only a small number was published.

Read before the Section on Dermatology and Syphilology at the 102d Annual Meeting of the American Medical Association, New York, June 4, 1953.

ing the five years and take a chance, even if a small one, of a permanent disfigurement." He suggests treating all lesions existing on the uncovered portions of the body, leaving others for surgical treatment later if they do not disappear.

If one notes the trend of present-day evening dresses, Bikini bathing suits, and costumes for fan and bubble dances, the logical question of what is meant by "uncovered portions" might be considered.

Ronchese,* in referring to his paper read at the International Congress of Dermatology, in 1952, wrote, "My belief is that the spontaneous involution is the rule, and the persistence is the exception." His views expressed previously do not seem to have changed basically, since he would seriously consider expectant treatment of lesions on the covered portions of the body.

Potter [6] is of the opinion that "hemangiomas are observed more often than any other variety of tumor in the newborn infants." Andrews and his colleagues expressed clearly their experience that many cavernous hemangiomas do not spontaneously regress. "It is much safer to treat them effectively at once and thus prevent all danger of their growing larger, ulcerating and seriously threatening the child with disfigurement."

ADVISABILITY OF EARLY TREATMENT

Since there is such confusion of thought among dermatologists, it is not surprising that the family physician, the pediatrician, and, above all, the distracted parents are in need of a guide or "rule of thumb."

Obviously, there is no such infallible rule. As Ronchese * so wisely stated, "There is nothing worse that absolutism in any field, and especially in medicine." A true statistical count of the percentage of hemangiomas that will spontaneously disappear cannot be made, short of taking a census of every baby born, say in the United States, over a given period of time, noting the original number that had hemangiomas at birth or shortly thereafter, and obtaining a complete and accurate follow-up of cases of untreated hemangiomas persisting into adulthood. The lesion present at birth or shortly afterward should be properly classified and recorded as cavernous or noncavernous. Furthermore, the type and amount of treatment administered is important and should be recorded; after all, treatment, conversely implied in the title of this paper, presumes adequate and proper treatment. Nowadays, it is probable that a large majority of hemangiomas are treated in some manner. Advice from the family physician or pediatrician to wait is often ignored, and the parent takes the child to someone who will render treatment. Only after accurate statistical studies, including careful classification of lesions and recording of treatment, would a clear-cut knowledge of hemangiomas be gained.

Certainly, a large percentage of cavernous hemangiomas do disappear spontaneously. It is probable that most noncavernous, or so-called strawberry, nevi disappear spontaneously. This paper is not directly concerned with the port-wine stain, a lesion that responds poorly, if at all, to irradiation. (However, plastic surgery, tattooing, or sandpapering offer much in the treatment of many cases of port-wine stain and hypertrophic naevus flammeus).

* Ronchese, F.: Personal communication to the author.

As is shown in the Figures, the physician who advises, "wait, the lesion will (or may) go away" must bear the moral responsibility for those cases of hemangiomas which refuse to be "wished away" and which persist into adulthood. For-

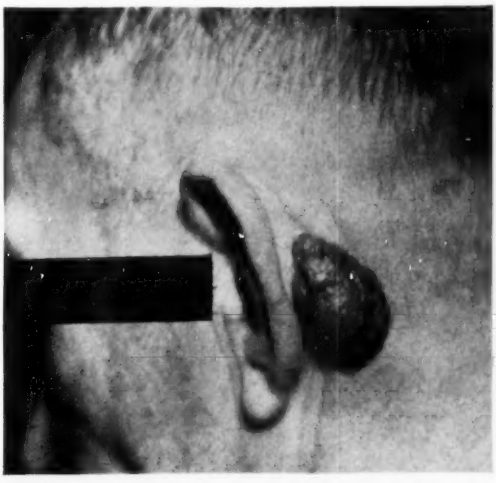

Fig. 1.—Hypertrophic naevus flammeus in a man aged 47. Simple destruction by electrosurgery at any time in life would have eradicated this lesion. Courtesy of Dr. John Lamb.

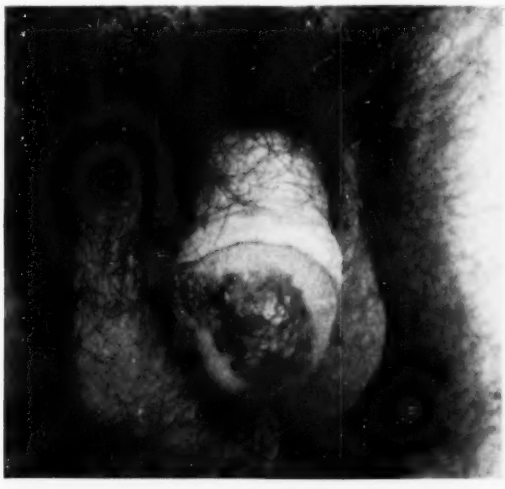

Fig. 2.—Cavernous hemangioma versus hypertrophic naevus flammeus in a man aged 20. Cryotherapy or superficial desiccation would have sufficed.

tunately, or unfortunately, the physician seldom sees his own patient at the time his prediction has gone awry, since time and transientness may have intervened to save him this chagrin.

It is generally agreed among most dermatologists that irradiation is the treatment of choice for cavernous hemangiomas, but only if given at an early age. The best and quickest results are obtained if treatment is begun prior to the third month of life, when the endothelial cells of the vascular channels are still immature. Certainly, the more these cells histologically resemble the mature endothelial cell, the more radioresistant they are.

Fig. 3.—Above, strawberry angioma in a woman aged 38. Below, mixed strawberry and cavernous hemangioma in a man aged 40.

The medical profession is justly proud of its cognizance of and efforts in the field of preventive medicine. It would seem that the problem of cavernous hemangiomas in infants properly belongs in this field. Very few procedures in medicine are specific. If one advises prophylactic tonsillectomies and prophylactic extraction of wisdom teeth, why isn't one justified in advising prophylactic treatment of hemangiomas?

The potential sequalae of persistent hemangiomas are manifold. First, the effect of an unsightly lesion can be devastating to the personality at a time when this profound facet of the individual is like soft wax and may be scarred for life. Second, the lesion may be contiguous to vital regions or organs (for example, the eye, mouth, vulva, or joints). Third, later treatment may be inadequate or incorrect; for example, irradiation after histologic maturity may be pushed past the point of tolerance.

Fig. 4.—Hemangioma in a woman aged 64. The lesion was of strawberry type until the first pregnancy, at the age of 24, when it became cavernous and remained so.

Fig. 5.—Lesion in a man aged 20. Irradiation in infancy or sclerosing agents should have eradicated this lesion easily. Courtesy of Dr. John Lamb.

Fourth, surgical remedy at best is often hazardous and cosmetically less than perfectly satisfactory. Fifth, persistence may produce incongruity of growth of the contiguous member. Sixth, ulceration with subsequent scarring may occur.

Even if, for the sake of argument, the percentage of hemangiomas that persist without treatment is infinitesimally small (which it is not) it looms extremely large if the person in whom the lesion persists is you, your child, or your patient.

Discussion of the various techniques of treating hemangiomas is well covered in the literature, as stated. However, certain pertinent observations may be noted.

In the ordinary and usual case, it is doubtful that the use of gamma radium has any particular advantage over the use of x-rays. A hemangioma overlying the

Fig. 6.—Man aged 30. Surely, irradiation in infancy or sclerosing agents should have benefited this patient. Courtesy of Dr. Truman Blocker.

Fig. 7.—Cavernous hemangioma on back of the neck in a man aged 50. Excision or destruction by desiccation would have eliminated danger of hemorrhage after trauma. Response to irradiation in infancy would have been gratifying. Courtesy of Dr. John Lamb.

growth center of a bone may best be treated with gamma radium, since the radiation from such a source "falls off" very rapidly, and less effective radiation is likely to reach the growth center, as would be expected from x-rays. On the other hand, a hemangioma which is rather large in area would best be treated with x-rays. In the

first place, the quantity of radium and the time consumed make the use of this modality impractical. Furthermore, the effective radiation reaching the lesion is more evenly dispersed to it than from several point sources of radium.

One error, not infrequently seen in cases of hemangioma treated with x-rays, is resultant clearing of the lesion in the center and retention of hemangiomatous

Fig. 8.—Cavernous hemangiomata, which, when first seen by a physician, were dime-sized. The parents were advised not to have the lesions treated. Ulceration and scarring could probably have been prevented by early treatment. Radium treatment, finally given in both cases, completely eradicated the hemangioma. Courtesy of Dr. Geo. C. Andrews.

tissue at the periphery. This may be attributed to the use during treatment of a shield which is too small. The treated area should include 5 to 10 mm. of normal skin around the hemangioma.

While it is true that one should judiciously withhold treatment once beginning regression is definite, I feel that any lesion which merits treatment at all will require

Fig. 9. — Cavernous hemangioma, dime-sized when first seen by physician. As in the cases shown in Figure 8, the parents were advised against treatment. The lesion did not ulcerate but, as seen, grew to a tremendous size. Radium treatment finally eradicated the hemangioma. Courtesy of Dr. Geo. C. Andrews.

Fig. 10.—Girl aged 16. By use of an eye shield, this cavernous hemangioma could have easily been treated with irradiation. Courtesy of Dr. G. C. Andrews.

at least two treatments. Accordingly, the second treatment may be given two weeks after the first treatment. Thus, one will be giving the second treatment to vascular walls which are in a mild stage of vasculitis, and with more effect. It would seem that infrequent treatment (every three or four months) only serves to "vaccinate"

Fig. 11.—Above, hypertrophic naevus flammeus in a man aged 35. Desiccation or plastic surgery could have saved this patient such a cosmetic defect. Below, cavernous hemangioma versus hypertrophic naevus flammeus in a man aged 45. Sclerosing agents plus cryotherapy should have benefited this lesion. Courtesy of Dr. John Lamb.

the endothelial cells and make them radioresistant, as well as allowing time to accomplish the latter purpose.

Although many cavernous hemangiomas will ulcerate spontaneously, it is probable that this complication is hastened by the exclusive use of unfiltered radiation early in the course of treatment.

Risk of ulceration of cavernous hemangiomas is also enhanced by the use of solid carbon dioxide in the early state of treatment. This agent is effective and safe to use toward the end of treatment as a "touching-up" measure to obliterate remaining strawberry portions of the growth. A purely strawberry angioma is best treated with this agent alone.

CONCLUSIONS AND SUMMARY

The foregoing discussion, by reviewing some of the pertinent expressions in the literature, points up the extremes in opinion regarding treatment of hemangiomas in infants. No reasonable scientific or statistical study is likely to yield a final, factual answer as to how many or which infantile hemangiomas will spontaneously regress.

The cases shown are mute evidence that hemangiomas can and often do persist.

It is doubtful that many parents will accept the advice to wait for spontaneous disappearance. Consequently, most lesions possessing an appreciable amount of cavernous element are sooner or later, often too late, treated in some manner. Thus, the family physician or pediatrician may allow to slip the opportunity to advise proper treatment at the optimum time.

For all the reasons set forth previously, it is my fervent belief that all hemangiomas showing appreciable cavernous element should have treatment, preferably irradiation, started prior to the third month of life. In advising such treatment, the physician correctly recognizes the problem as one of preventive medicine.

ABSTRACT OF DISCUSSION

Dr. F. Ronchese, Providence, R. I.: I became interested in the spontaneous involution of hemangiomata after reading Lister's paper, a decade or so ago. To convince myself, I followed up as many untreated cases as I was able to find. This is a difficult task, like any study made over a period of years for a condition in which treatment, in one form or another, is the rule, and nontreatment the exception.

The spontaneous involution and the persistence through life are both established facts, although the respective percentages are difficult to evaluate. The main problems remain: Should all hemangiomata be treated? Are there cases in which no treatment is indicated?

The sex, location, size, and appearance are elements to be considered in deciding on no therapy. I believe that hemangiomata of the vulva, scrotum, buttocks, breast, female scalp, palms, or soles, can be left untreated. If spontaneous involution fails to materialize, surgery can be done later in life or the hemangiomata can be left alone.

The persistence of a certain number of hemangiomata through life, on the other hand, may justify the advice of therapy for all.

I wish emphatically to agree with Dr. McCuistion that the treatment "must be the proper one."

What is "proper treatment"? Among experts there are not two having the same idea in treating a given case. However, when there is experience, usually, no harm is done. This is most important. When there is no experience, considerable harm may be done if, for instance, a physician undertakes to treat a hemangioma by reading the half-page a textbook devotes to the therapy of this condition, rents some radium, and applies it. It seems fantastic, but it is done. Then come the frightful sequelae: The radium is blamed for it and its use proclaimed dangerous. Of course it is dangerous in unskilled hands.

There are no two hemangiomata alike. Every case is a new therapeutic problem. There is no textbook or paper from which to receive help in handling the case. The only help comes from proper training and experience. The disasters following improper therapy are a great comfort to the advocates of no therapy for all.

I believe the dermatologist is the specialist most qualified to treat or to outline the treatment of hemangiomata, in cases, for instance, in which surgery is preferable to use of radium, x-rays, or sclerosing fluids, or to no therapy, in a given case.

Irradiation is one form of therapy which has its indications. However, I believe that radiation should not be used if the same results are expected with other methods. In the case of the strawberry type 1 or 2 by 2 cm. in diameter, 1 or 2 mm. in elevation, often one application of carbon dioxide easily produces a satisfactory cure.

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Clinical Notes, New Instruments and Techniques

TREATMENT OF PERIUNGUAL WARTS

COLONEL GEORGE PRAZAK
AND
CAPTAIN M. PAUL LAZAR
MEDICAL CORPS, UNITED STATES ARMY

Many of us have had treatment problems related to periungual warts. Frank's technique was employed by us with some success, but it was found that one addition to the management of these verrucae aided us a great deal.[1]

The regimen is as follows:

1. Full-strength trichloroacetic acid is applied to the wart and allowed to dry.
2. A piece of 40% salicylic acid plaster in the shape of the wart is applied over the lesion.
3. The entire distal phalanx is covered with an occlusive adhesive tape dressing.
4. One week later the tape is removed, and in many instances the wart may be removed easily by curettage.

At times the maceration is extensive, and one may find that 24 hours of exposure to the air may aid in differentiating the wart from normal tissue before curettage is instituted. In several cases a second treatment was necessary, though in most of the cases cure was obtained with one application.

Previous surgery and other types of therapy did not appear to preclude our obtaining a successful result in each instance. Furthermore, none of the 13 patients treated complained about the treatment or experienced any discomfort, though one can readily visualize infection or local fissuring causing distress.

The management of periungual warts in which a modification of Frank's method gave us excellent results is being reported because of the difficulties encountered in treating this condition.

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From the Dermatological Service, Osaka Army Hospital (Col. James Turner, M. C., Commanding Officer, and Col. George Prazak, M. C., Chief).

Correspondence

NIKOLSKY SIGN

To the Editor:—In the interesting paper on Nikolsky Sign (A. M. A. Arch. Dermat. & Syph. **68**:334, 1953) Dr. Herman Goodman stated "available biographical sources failed to disclose any date of death. . . . It is assumed that Dr. Nikolsky is dead." Nikolsky died in March of 1940. This is disclosed in a paper by P. V. Kozhevnikov in the *Vestnik venereologii i dermatologii no. 3*, May-June, 1950, pp. 33-34. This paper is entitled "The Contributions of P. V. Nikolsky to Soviet Dermatology and Venereology." Kozhevnikov also gives the correct *curriculum vitae* of Nikolsky. Nikolsky was born in 1858 and died in 1940. In 1885, he received his medical degree from the University of Kiev-Saint Vladimir Medical School. He published his famous thesis on pemphigus in 1895. In 1900, he was appointed Professor and Head of the Department of Dermatology at the University of Warsaw. He remained in Warsaw until 1915, when the Medical School was evacuated during World War I and transferred to the interior of Russia, Rostov on the Don. He remained in Rostov until 1931 when he was retired as Professor Emeritus. His last public appearance was in 1935 at the Budapest International Dermatologic Congress, where he read a paper on the History of Dermatology in Russia. Kozhevnikov credits Nikolsky incorrectly with being the first to describe trichorrhexis areata (Sabouraud) and cutis rhomboidalis nuchae (Jadassohn). This is the unfortunate tendency of contemporary Russian literature to credit Russians with discoveries that do not belong to them. Nikolsky was a great teacher and an honest man, and his place in the history of dermatology is secure. He earned it by his own contributions to the sum total of world knowledge.

Samuel J. Zakon, M.D., Chicago.

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

Irving L. Schonberg, M.D., *President*

John R. Haserick, M.D., *Secretary*

George M. Stroud, M.D., *Reporter*

May 21, 1953

Ehlers-Danlos Syndrome Associated with Exfoliation of Palms and Soles. Presented by Dr. H. A. Haynes Jr. and Dr. William C. Marsh.

Brothers, D. C., aged 14 months, and P. C., aged 2½ years, were seen because of the chief complaint that at the age of 3 months both developed mild redness and continuing sheets of desquamation from the palms and soles. Examination revealed hypermobility of the joints, dermatochalasis, and scattered ecchymoses. The mother stated that many areas of peeling are preceded by "water blisters"; the father has never seen these.

The family history revealed that the mother is "double jointed" and that in her high school days as a cheer leader she suffered aching joints after violent exercise.

Although Ronchese has reported an epidermolysis-bullosa-like eruption of the hands and feet, no reference can be found to continued exfoliation associated with Ehlers-Danlos syndrome.

DISCUSSION

Dr. H. A. Haynes Jr.: I think the diagnosis is open to question. These cases were seen the day before yesterday for the first time. There is some question as to whether or not the peeling, which continues in a more or less severe degree, is preceded by bullae, or whether it appears without the advent of a bulla. The mother says that the child has frequent blisters, and the father has never seen any. Some of the lesions look like dried bullae now, and some of the areas of exfoliation do not seem as though they were subsequent to a previous bulla. If they are always preceded by bullae, it is apparently an epidermolysis eruption as described, but if there is desquamation without bullae it is a new entity. It is also interesting that in both children it began at their respective ages of 3 months. There is a long family history, which goes back to the great-grandmother of the children. I have seen other cases of Ehlers-Danlos syndrome, but none had desquamation of the palms and the soles.

Kerion with Id Reaction. Presented by Dr. A. L. Leiby.

C. R., a 4-year-old girl, who lives on a farm, was noted to have a round spot on her left arm on March 4, 1953. On March 19 the lesions had appeared on her chest, nose, chin, forehead, and scalp. The patient did not seem to be troubled by her condition, except for a marked tenderness of her scalp.

Physical examination revealed a large tumor mass on the upper left forehead, extending onto the scalp. A viscid, semitransparent fluid exuded over matted hairs. There was a small tumor on the right forehead. Coin-sized circumscribed reddish circles with clearing centers and furfuraceous scaling borders were presented on the left side of the nose, left side of the mouth, under the chin, on the medial aspect of the left cubital area, and on the left forearm.

M. R., a 10-year-old sister, presented similar lesions on the face, right scapula, right shoulder, and medial right thigh. The lesion on the right thigh was about 5 cm. in diameter.

A culture from the 10-year-old girl, similar to the culture I made on April 6, was sent to Dr. George M. Lewis, who identified it as a type of Aspergillus. Its tannish-gray color was in contrast to that of the sister, whose culture was black and identified as Aspergillus niger.

Treatment was started on March 19 and consisted of undecylenic acid ointment. On March 25 a salicylanilide ointment was substituted, and potassium permanganate compresses were

advised. On April 6 the younger patient developed a generalized discrete papular eruption and slight fever. The lesions have begun to fade out and now have a tannish-brown color. The kerion persisted and on April 28 a sulfonamide drug was prescribed, and there has been a rapid decrease in the size of the kerion. An area of alopecia is present in the left frontal region.

DISCUSSION

DR. J. A. GAMMEL: I think it is rather difficult to associate the Aspergillus with the eruption. In order to do that we have to have more than cultures. At least four or five culture tubes should be inoculated with four to five minute particles of the areas. If we find Aspergillus in a good number of them and if biopsies of the kerion show Aspergillus heads in the section it would be added evidence, but otherwise we have to consider these organisms as contaminants. To prove that they are pathogenic one has to find them repeatedly in a number of inoculations from the various parts of the lesion and various parts of the body and, if possible, in sections.

DR. A. L. LEIBY: So far as the Aspergillus is concerned, while Lewis claims that they are not pathogenic, there are some men who do. An interesting point is the fact that the condition developed after the 4-year-old got manure on her head. The mother said that while she was shoveling manure the child accidentally received a load of it on her scalp. The mother merely brushed it off. In the office I have never cultured Aspergillus as a contaminant. I assume, therefore, that the organism in these cases is not a contaminant. I think that the two girls were infected with the same genus but a different species of Aspergillus, which was pathogenic.

DR. J. A. GAMMEL: Did you use foreign-protein therapy, such as typhoid? I think that works very well in cases of kerion.

Pemphigus Vulgaris. Presented by DR. FRANK M. MCDONALD, Akron, Ohio.

A. P., a white woman aged 65, is presented because of a severe bullous inflammation of the ankles. Approximately nine months ago a 1 by 1 cm. bleb appeared on the anterior aspect of the left ankle. The process soon became eczematous. This was diagnosed as a pyogenic dermatitis, and it responded to appropriate therapy. The right ankle became similarly involved four months later and responded to treatment. Recently the eruption has recurred.

For the past 30 years the patient has had generalized rheumatoid arthritis, which has been sufficiently severe for the past 12 years to confine her to bed or a wheel chair. Lymphedema has been present on the legs for about one year. The arthritis has been treated with cortisone for the past two years in doses of approximately 50 mg. per day. Barbiturates have been administered intermittently for the past five months. There is no history of other drug ingestion.

Examination of the skin shows various sized bullae on both ankles. Some of these appear on inflamed skin, others on normal-appearing skin. Moderate sustained pressure on the bullae forces the fluid forward as a pseudopod without rupturing the blister. A single ruptured bulla is found on the left buccal mucosa.

Urinalysis was normal except for erythrocytes, 20 to 30 per high power field. The hemoglobin was 81%; the red cells numbered 4,800,000 per cubic millimeter and the white cells 10,000, and the differential count was normal. The sedimentation rate after 15, 30, 45, and 60 minutes was 1, 5.5, 16, and 18 mm. The fasting blood sugar was 108 mg. per 100 cc. Serum proteins were 6.4 gm. per 100 cc., with a ratio of 1:1. The basal metabolic rate was + 39.

Treatment with erythromycin, sulfamerazine, sulfapyridine, and chlorprophenpyridamine (Chlor-Trimeton) orally has been ineffective. Warm boric acid solution compresses topically have been comforting, and pyoderma has been minimal.

DISCUSSION

DR. G. M. STROUD: I was intrigued by the history in that after the patient took cortisone by mouth in fair dosage for two years for rheumatoid arthritis, the pemphigus, which usually responds to cortisone, developed. It reminds me of a case I saw yesterday of eczema treated successfully by an internist with hydrocortisone (Hydrocortone) ointment for over a week, and then overnight the eczema recurred to a more extreme degree than ever previously. It

makes me wonder whether giving this drug internally or using it locally does not do something to the defense mechanism which necessitates a greater need for cortisone than ordinarily would occur.

DR. J. A. GAMMEL: This patient had a positive Nikolsky sign.

DR. F. M. MCDONALD: This patient was presented for a variety of reasons. As Dr. Stroud pointed out, her bullous disease developed after she had received cortisone for two years for her arthritis. Secondly, her bullae remained localized to the lower legs, ankles, and dorsa of the feet until three weeks ago, when a bulla was seen on the left buccal membrane. I also was intrigued by the elevated basal metabolic rate of + 39 which she presented, because the findings in her case resemble to a fair degree the findings in two cases of pemphigus in rubber workers presented last month at the Cleveland Clinic. This patient had no such exposure and did not show the symptoms usually found in other bullous diseases.

Pemphigus Vulgaris. Presented by DR. FRANK M. MCDONALD, Akron, Ohio.
Generalized Lichen Planus. Presented by DR. A. L. LEIBY.
Erythema Perstans. Presented by DR. A. L. LEIBY.
Localized Scleroderma. Presented by DR. FRANK M. MCDONALD, Akron, Ohio.
Sarcoidosis. Acne Vulgaris. Presented by DR. H. A. HAYNES JR. and DR. WILLIAM C. MARSH.
Urticaria Pigmentosa. Presented by DR. H. A. HAYNES JR. and DR. WILLIAM C. MARSH.
Epidermolysis Bullosa. Atopic Eczema. Presented by DR. H. A. HAYNES JR. and DR. WILLIAM C. MARSH.
Atopic Eczema with Marked Wrinkling of Face and Neck. Presented by DR. A. L. LEIBY.
Erythema Induratum. Presented by DR. FRANK M. MCDONALD.
Keratosis Pilaris. Presented by DR. FRANK M. MCDONALD.
Case for Diagnosis (Dermatitis Herpetiformis? Lichen Planus? Bullous Erythema Multiforme?). Presented by DR. H. A. HAYNES JR. and DR. WILLIAM C. MARSH.

JOINT MEETING OF METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES AND LOS ANGELES DERMATOLOGICAL SOCIETY

Metropolitan Dermatological Society of Los Angeles

Stanton B. May, M.D., *President*

Fred F. Feldman, M.D., *Vice-President*

Irving A. Lewe, M.D., *Secretary*

Los Angeles Dermatological Society

Walter Schwartz, M.D., *President*

J. Walter Wilson, M.D., *Secretary*

April 28, 1953

Xeroderma Pigmentosum (?) in a Negro. Presented by DR. MAXIMILIAN E. OBERMAYER and DR. MARGARET A. STORKAN.

Mrs. L. A., a 24-year-old woman consulted us in July, 1951, because of an eruption of her face, neck, and hands, which was present for many years. At birth her hair was red and she had many "freckles." Her hair gradually became darker, and her "freckles" have increased in number. From her earliest recollection she has always protected herself from the sun, as any exposure will give her redness and increase the number of "freckles." There have been no changes of color in the urine and no pertinent systemic complaints.

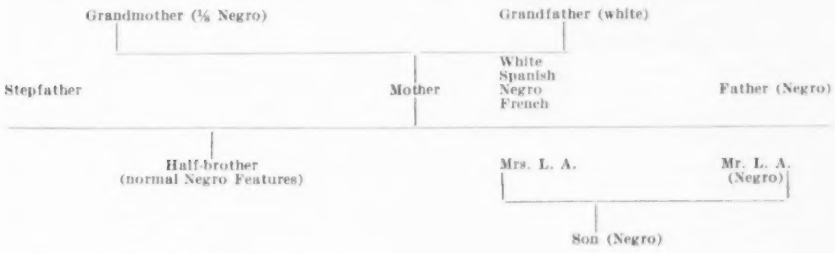
Examination discloses a well-developed and well-nourished brown-eyed Negro woman with straight hair. The skin of the face is slightly thickened and shows areas of scaling. Scattered on her face, the V-area of the sternum, dorsa of hands, and forearms are lentigines. On the bridge and tip of the nose are several firm papules varied in size and shape, the largest measuring 5 mm. The specimen for biopsy was removed from one of these elevated lesions.

Microscopic examination of the specimen taken for biopsy revealed a dissolution of the epidermodermal junction, with collections of basophilic staining cells (like basal cells) in the pigmented area. The cutis is composed of small capillaries and scattered basophilic cells,

some of which are spindle-shaped, with deep blue-staining nuclei. There are no appendages present. The sections stained for pigment revealed the presence of melanin in the upper portion of the cutis.

In addition to sun-protective creams the patient has received a nonvirilizing oral testosterone preparation (Methostan, Schering). The patient has expressed the belief that the disorder becomes more pronounced when she does not take the tablets.

The patient stated that her family tree in regard to racial background was as follows:



The patient describes her family thus:

Mother: straight hair, classic "Italian" features.

Father: unknown family background, but freckled, dark skin, Negroid hair type.

Son: Negro features and hair type with no freckling.

DISCUSSION

DR. ARTHUR FLETCHER HALL JR.: I was surprised to read in the protocol that this woman is Negro. She has no negroid features, she had red hair as a youngster, and she still has straight hair. Skin carcinoma of the exposed areas is rare in Negroes and that may be because Negroes do not develop their pigment as a response to exposure to sunlight, but are born equipped with it by heredity. Apparently, in this woman what pigment she has did develop as a response to sunlight—what Negroid pigment she has is very little indeed.

What has developed in response to sunlight is excessive "freckling" plus what I believe to be some basal-cell carcinomas on the nose. The "freckling" did not develop on her nose (thereby depriving that skin area of protection from sunlight) but developed elsewhere, and where the "freckling" has developed, I see no evidence of carcinoma or xeroderma.

I believe that the fact that this woman carries some Negro inheritance is purely coincidental, and I do not believe it has any bearing on the pigmentation that she shows. The interesting thing about it is that in response to exposure to sunlight, which her skin is not hereditarily prepared to cope with, her skin has attempted to defend itself in some areas by the production of "freckling." In those areas that have not been able to defend themselves carcinomas are developing.

Now the rest of her skin, clinically, does not show atrophy, telangiectasia, or keratoses. Whether the irregular pigment formation has been of any use in defense, I do not know. I should like to have someone who knows about it tell me about some biopsy specimen staining for pigment from areas scattered over her face which will not suggest "bigger and better" biopsy specimens in this case. The Negro ordinarily gets a defense by pigment that has gone upward in the prickle-cell layer from the basal-cell layer, progressing upward and outward with the process of normal keratinization. The white man does not. His pigment does not go upward and outward to any extent that is enough to protect him from sunlight but usually "drops off into the dermis." I believe that is what is happening in this woman. She has not inherited the tendency or ability to push her pigment on out from the basal-cell layer; her Negroid inheritance has not helped her. What confuses the issue is that the biopsy specimen I looked at, I am not able to identify as out-and-out carcinoma of either a basal-cell or squamous-cell type. What I did see suggests an adnexal type of thing—a lot of fibrosis. I should like to hear what Dr. Winer has to say about the histological appearance of the biopsy specimens of this case.

DR. LOUIS H. WINER: The series of biopsy specimens removed from this patient for the past four years indicate all the changes which have occurred in this patient. They began with neoplasia and are now concluding with fibrosis and keloid formation.

DR. JOHN W. CARNEY: This is the first case of xeroderma pigmentosum that I have seen in a Negro. I think that this is a case of extreme interest in that it touches upon the problem as to which persons should be included under the term Negro. In America this term is applied both to persons of decided African origin and to those who have little or no perceptible Negroid features but do have Negro ancestry. Anthropologically, the "true Negro" is the African Negro. I raise this point because of the statement which one reads so frequently: "Contact dermatitis and light sensitivity dermatoses in the Negro are uncommon." I do not feel that this statement is correct unless one is speaking of the prevalence of these diseases in a "true" Negro. Dermatologists and skin clinics having a large Negro clientele will find ample examples percentage-wise of eczematous contact-type dermatitis, and the usual photosensitive dermatoses. Some of the literature of 30 to 40 years ago states that lupus erythematosus is rare in the Negro; we certainly know now that far from being rare, it is a very frequent finding.

If the patient presented tonight is to be classified as a "Negro," then more definitively, she is of the Creole type that is present in Louisiana. The Creoles usually have a mixture of Negro, French, Indian, and/or Spanish blood.

DR. J. WALTER WILSON: Is resistance to light a function of the depth of pigmentation? Also susceptibility to contact dermatitis—is that also a function of the depth of pigmentation or not?

DR. JOHN W. CARNEY: No, other factors besides depth of pigmentation function in the skin's resistance to light.

DR. HAROLD C. FISHMAN: I think xeroderma pigmentosum is a recessive genetic characteristic which rarely occurs in Negroes, but this woman is not a true Negro. I think this is xeroderma in a patient with parentage which allowed the recessive characteristics to appear on both sides of the family tree. This is most unusual. I think the tumor is a true sarcoma and not a carcinoma.

DR. LOUIS H. WINER: I agree with Dr. Carney that histologically, pigment of the Negroid type is not limited to Negroes. Mexicans, Indians, Chinese, and Filipinos all have epidermal pigmentation as do the Negroes. I have seen xeroderma pigmentosum in the case of a Mexican girl, presented to the San Diego Dermatological Society meeting by Dr. Walter Nickel in 1948. This patient later developed pigmented basal-cell carcinoma. Dr. Obermayer's case might well be an aberrant form of xeroderma pigmentosum in which epidermal hyperplasia and connective tissue hyperplasia existed at different times.

DR. ARTHUR FLETCHER HALL JR.: I believe that the main feature that protects Negroes from contact dermatitis (of the sensitization type as well as primary irritation) and also to a great extent from sunlight is the thickness of the stratum corneum; the hereditary pigment also protects the Negro from sunlight but probably contributes little or nothing toward protection from contact dermatitis. The white man who is capable of "tanning," without any (Negroid) hereditary tendency to spew his pigment up toward the stratum corneum, is protected from sunlight purely by increasing the thickness of the stratum corneum, and it has been demonstrated experimentally on humans and on animals that the stratum corneum will increase in thickness as much as sevenfold in individuals who are capable of tanning, as a result of repeated exposures to sunlight. Pity the poor Irishman who burns and peels off all those layers instead of piling them up, thereby developing no defense.

DR. MAXIMILIAN E. OBERMAYER: I feel that the low incidence of cutaneous carcinoma in the Negro cannot be explained by such features alone as hyperpigmentation or increased thickness of the stratum corneum. If this patient were Caucasian, she would probably have died of her disease by now. Since she is of mixed stock, containing Negro and Indian blood, it is more likely that the protection stems from her racial genes rather than from the actual structure of her skin. I was surprised to hear one discusser speak of the carcinoma of her nose. The microscopic features of the sections were those found on weather-beaten skin. I think that the prognosis in this case is fair if protection against sunlight is consistently practiced.

DR. MARGARET ANN STORKAN: The patient's father is a Negro and she has sisters who are blonde and some are blue-eyed. Also she has paternal aunts and cousins who have red hair; some are freckled, some are not. Her own son at birth had sandy-colored hair. At 6 to 8 months of age she noticed changes in his skin, and as the child grew older, he assumed his father's Negroid characteristics.

Reticulum Cell Type of Lymphosarcoma. Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

Bullous Lichen Sclerosis et Atrophicus(?). Presented by DR. BEN A. NEWMAN and DR. FRED F. FELDMAN.

Case for Diagnosis: Pustular Psoriasis? Dermatitis Repens? Presented by DR. MEYER BERKE. (Presented for therapeutic suggestions.)

Tinea Profunda. Presented by DR. SAMUEL AYERS JR. and DR. SAMUEL AYRES III.

Mycosis Fungoides D'emblée (Gigantea). Presented by DR. NELSON PAUL ANDERSON.

Case for Diagnosis: Allergic Granuloma? Presented by DR. MAXIMILIAN E. OBERMAYER, DR. MEYER BERKE, and DR. JOSEPH TRAUB (by invitation).

Lichen Spinulosis et Folliculitis Decalvans (After Treatment with Vitamin A). Presented by DR. FLETCHER HALL.

Case for Diagnosis. Presented by DR. STANTON B. MAY.

Dermatomyositis. Presented by DR. STANTON B. MAY.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Marion B. Sulzberger, M.D., *Chairman*

J. Lowry Miller, M.D., *Secretary*

April 7, 1953

Sclerema Neonatorum. Subcutaneous Fat Necrosis. Presented by DR. LESLIE P. BARKER.

A Negro girl, aged 5 months, has hardness of the buttocks of two days' duration. The infant was admitted to St. Luke's Hospital because of an inflammatory hardness of the buttocks and lower back of two days' duration. On admission the child was 10 days old; she had been delivered by Caesarean section following 26 hours of nonprogressing labor. The patient had never been breast fed. While in the hospital the infant received three daily intragluteal injections of penicillin for pneumonitis. The day after taking the baby home the mother noticed both buttocks were hard, and the hardness spread up over the back and posterior thighs.

Mother had two other children, 25 and 27 years old. On admission the infant, 10 days old, appeared to be a well-developed and nourished Negro baby, in no acute distress but irritable when handled. General examination normal except for the cutaneous and subcutaneous areas of "board-like" infiltration involving both buttocks, the lower half of back, upper part of both thighs posteriorly and upper part of both arms. No increased heat or apparent tenderness in areas. Temperature varied between 99 and 100 F.

Complete laboratory work-up including EKG, x-rays of chest, abdomen, skull, and extremities, urine analysis, blood chemistry, and throat cultures were all normal.

Blood count was normal except for 15,200 WBC with 3% eosinophiles.

Section of hair-bearing skin showed the skin to be normal. The subcutaneous tissue contained adipose cells and crystalline-like clefts which were compressing the adjacent connective tissue but did not have a distinct capsule. There were several areas of hemorrhage within the adipose cell clusters. The fat cells were large and appeared nonviable, but with well-preserved cellular outlines. Many of the cells were filled with slit-like spaces which had the appearance of needles or thin plates, and there were small areas of calcium material in the regions of most cellular destruction. There were occasional areas surrounding inflammatory reaction, with the presence of monocytes and lymphocytes in the periphery.

The infiltration gradually spread in plaque-like fashion to involve the entire back and sides of trunk, the original areas becoming less infiltrated. The child is now 5 months old, and most of the infiltration has disappeared from the trunk and arms but is spreading down the legs. Child is gaining weight and apparently feels fine.

DISCUSSION

DR. DAVID BLOOM: This is a case of subcutaneous fat necrosis of the newborn, which is not rare. It is seen in children that are large and exposed to trauma during delivery or who have to be resuscitated. The prognosis is good. In sclerema neonatorum the child is often a premature baby, small, dehydrated, and the prognosis is poor.

DR. FREDERICK REISS: I agree with Dr. Bloom, the characteristics of sclerema neonatorum are not present here. It is a progressively fatal disease, and children that are affected with sclerema neonatorum hardly survivie two or three months. The skin of these children is atrophic, wrinkled, and they are cadaverous looking; in this case these symptoms are absent.

DR. MAURICE J. COSTELLO: I had an opportunity some years ago to see a number of these cases with Dr. Howard Fox, who described them so beautifully, and I have seen a number of cases since that time. I do not think it is quite true that birth-pressure trauma has a great deal to do with this because one sees it in children who are born by Caesarean section. The lesions are as a rule on the extensor surfaces, the buttocks and the shoulders, and the back. The only thing that puzzles me in regard to the case presented by Dr. Barker is the fact that these phlegmon-like infiltrations are still present. The biopsy proves it is subcutaneous fat necrosis of the newborn, and I agree with Dr. Bloom and others that it is not sclerema.

DR. ORLANDO CANIZARES: I agree with Dr. Costello that history of trauma is not always present in these cases. Recently at St. Vincent's Hospital I saw five or six patients with lesions similar to this one. In one of them the lesions were fluctuating. For this reason the lesion was diagnosed as an abscess by a surgeon, and, when seen, the patient had already been scheduled for an operation, which of course was cancelled.

DR. GERALD F. MACHACEK: I showed two cases of adiponecrosis which occurred in children whose mothers were diabetic. I showed some fat necrosis in adults who were diabetics.

DR. LESLIE P. BARKER: I think sclerema neonatorum and subcutaneous fat necrosis of the newborn are the same disease. They are both subcutaneous fat necrosis. My reason for making a diagnosis of sclerema in this case was that the histology showed needle-like crystals in the fat cells.

I think trauma from the pencillin injections in the buttocks initiated this attack. We have a similar case in an adult after penicillin injections.

Pemphigus Vulgaris (In Remission with Symblepharon of the Left Eye)? Presented by DR. FREDERICK REISS.

H. W., 49-year-old woman, first observed 10 years ago small blisters formed on the hard palate, which made swallowing difficult because of pain in the above area. Several months later the left eye became inflamed, which produced "scarring." Patient was first seen at the skin clinic in December, 1952, at which time extensive blister formation and erosions were present on the tongue and in the fauces. Treatment consisted of weekly injections of suramin sodium (Naphuride). A total of 13 injections were given. Simultaneously, twice weekly, 40 mg. of corticotropin was administered, totalling 23 cc. After treatment was completed, all lesions had disappeared in the oral cavity; however, after the therapy was discontinued, tiny blisters reappeared on the hard palate, which responded favorably to potassium arsenite (Fowler's solution).

Physical examination revealed symblepharon of the left eye and a few tiny reddish spots on the hard palate. No lesions developed as yet, after 10 years, on the integument.

DISCUSSION

DR. HELEN CURTH: I believe the case was presented as pemphigus vulgaris with a question mark. We have to make a distinction between the ocular manifestations observed in pemphigus vulgaris and those in ocular pemphigus. I believe this is not pemphigus vulgaris because the ocular manifestation of pemphigus vulgaris is conjunctivitis, which this patient never had. Also the fact that she is in very good health and of Irish-German extraction would speak somewhat against pemphigus. This is a very mild case of symblepharon or ocular pemphigus

which should be better called essential shrinkage of the conjunctivae. I think, in addition, she has, as Dr. Reiss explained, lesions of herpes simplex, and I believe that some of the blisters in the oral cavity substantiate this diagnosis.

DR. MAURICE J. COSTELLO: I agree with Dr. Curth. This patient does not have pemphigus vulgaris. She has ocular pemphigus. Symblepharon is never seen in the vulgaris type. It is a common thing in ocular pemphigus. Almost invariably there are lesions at the junction of the hard and soft palates, on either side behind the last molar teeth, and she had such lesions. These lesions are fixed and they remain in these locations for a long time. Later on lesions may develop elsewhere and the eruption becomes generalized.

DR. ORLANDO CANIZARES: I agree with the previous speakers and I should like to request that we will make an effort to avoid the term "ocular pemphigus."

DR. DAVID BLOOM: It is true that symblepharon of the eye is associated with a bullous eruption which is more chronic and benign than pemphigus vulgaris in the strict sense of the word. Nevertheless, I believe that essentially we cannot definitely separate these eruptions from pemphigus vulgaris.

DR. GERALD F. MACHACEK: I am more confused than ever by the semantics. The fact that the woman is Irish does not rule out pemphigus. I think we have all seen people who were not Jewish, and who were not Italian, who had pemphigus.

DR. COSTELLO: I think that ocular pemphigus is a good term because the disease, as a rule, begins in the eye and remains there for years. It is sometimes referred to as essential shrinkage of the eyeball—conjunctiva. No one has encountered very many of these cases, but I have observed two patients with this type who died of generalized pemphigus. The disease has a fatal prognosis, certainly in half of the cases that I have seen. It is a serious disease because it causes blindness and eventually total blindness. By the way, pemphigus vulgaris lesions occur on bulbar and palpebral conjunctiva but these lesions do not cause scars or visual disturbances.

DR. REISS: I presented the case as pemphigus with a question mark. If I had labeled this case as an ocular pemphigus, the discussion would not have been as interesting. I fully agree that the two diseases are entirely different. However, I agree with Dr. Bloom that there may be some pathogenetic etiological relationship between the two. This may be true in this case also. This woman did not respond to any other previous treatment during the last six or seven years. However, after suramin sodium injections in combination with corticotropin the lesion in the oral cavity immediately responded. After these treatments were discontinued, the patient relapsed.

Acute Disseminated Lupus Erythematosus. Presented by DR. LESLIE P. BARKER for DR. VALENTINE C. BAKER.

U. V., Estonian woman, aged 30, complained of an eruption on facial area, elbows, hands, and clavicular area of three and one-half years' duration.

This patient felt perfectly well until three and one-half years ago, when she noticed the appearance of a rash on her ears, forehead, cheeks, nose, eyelids, calves, elbows, hands, clavicular and interscapular region. The cheek lesions formed a butterfly pattern across the bridge of the nose. The rash was accentuated by sunlight.

A few months after the onset of her skin condition she began to have pain in the left shoulder and in the finger joints. Patient has been treated at the Skin and Cancer Hospital with liver, bismuth, and arsenic trioxide, but without any benefit.

The midfacial area, the forehead, and the ears present erythematous, circumscribed scaly patches which are partially confluent. Similar lesions are also found on the sternum, the upper part of the back, both forearms, dorsa of hands and fingers. The scalp shows three areas of alopecia and absence of follicles. On the hard palate are erythematous lesions.

The right cervical and the right axillary nodes are palpable and tender.

A soft systolic murmur is heard over the apex.

Results of laboratory examinations (Sept. 15, 1952) were as follows: L. E. cells were found in the sternal marrow but not in the blood stream. Serologic test for syphilis, negative. Blood cell count: hemoglobin, 12.2 gm. per 100 cc. (84%); RBC, 4,040,000; WBC, 14,000,

with 79% polymorphonuclear leucocytes, 20% lymphocytes, and 1% eosinophiles. Urinalysis, negative. Blood chemistry: sugar, 90; total serum protein 6.8 gm. per 100 cc. (albumin 4.2 gm. and globulin 2.6 gm.); potassium, 16.7; plasma chlorides, 610; serum sodium, 327; sedimentation rate dropped from 22 to 4 while patient was receiving corticotropin I.V. Tuberculin tests, negative (1:10,000). Chest x-rays: densely calcified foci in both lung fields; no active infiltration in either lung; heart and mediastinal structures normal. X-rays of both hands: no bone or joint pathology seen. X-rays of abdomen: normal findings. Barium enema: no defects demonstrated.

Biopsy: There is a hyperkeratotic layer which is separated from the underlying portion of the epidermis by a thin pinkish-staining hyaline-like zone. There is a liquefying degeneration of the epidermis and vesicles filled with fluid; few polymorphonuclear leucocytes and histiocytes are seen. The basal layer and rete pegs of the epidermis are frayed. The upper layer of the dermis is infiltrated by monocytes and histiocytes. This infiltration extends into the epidermis in and about hair follicles and about blood vessels. This histology is consistent with lupus erythematosus.

Patient was given isoniazid (Nydrazid) 300 mg. daily from May 22, 1952, to June 16, 1952 (total 7,600 mg.). Under this treatment the lesions became less erythematous but patient still had joint pain.

From June 17, 1952, to Aug. 4, 1952, corticotropin, 80 mg., was given daily I.M. The joint pain disappeared within a few days and the general condition improved. On July 3, patient had a flare-up of her mouth lesions, which, however, subsided completely subsequently. The erythematous rash on face, forehead, and arms improved under corticotropin treatment. The blood count which showed a moderate anemia on admission returned to normal.

On Aug. 5, 1952, corticotropin was cancelled and cortisone, 75 mg. combined with 200 mg. of isoniazid, was given daily. She did very well while under this treatment and the lesions became markedly pigmented.

On Sept. 9, the medications were discontinued and four days later patient had anorexia, muscle pain, and recurrence of skin lesions. She was readmitted to St. Luke's Hospital, where she was successfully treated for 10 days with intravenous drips of corticotropin (25 mg. daily). The bright-reddish color of the lesions turned into brownish discoloration and the lesions decreased definitely in size within a few days.

From October until present patient has been followed at the dermatology clinic. She has done fairly well with cortisone therapy and liver extract. Because of reported improvement in a case of acute disseminated lupus erythematosus patient was given artichoke concentrate for the last two weeks, 9 tablets daily. This treatment was discontinued because of recurrence of joint pain and moderate extension of skin lesions.

DISCUSSION

DR. VICTOR H. WITTEN: I should like to ask Dr. Baker whether the laboratory studies were done at the time the patient was being given corticotropin or cortisone, or during the intervals between their administration.

DR. VALENTINE C. BAKER: I could not say but I do not think all the blood studies were reported. Some of them showed about 5,000 white blood cells, and then this one that was taken and gives 14,000. She was feeling rather well, and I think the blood counts varied considerably. She also had at different times a high sedimentation rate. The time it was taken was when her condition was better.

DR. VICTOR H. WITTEN: It is interesting that all the laboratory studies were negative in this case. The sedimentation rate had dropped, the A/G ratio was normal and there was no leucopenia. The only exception was the L.E. phenomenon, which was present in the sternal marrow but not present in the peripheral blood. Another test might be done. Watson, O'Leary, and Hargrave reported scraping the base of a cantharides blister and staining for the L.E. cell. They found peculiar neutrophilic leucocytes resembling the L.E. cell in instances in which the sternal marrow was negative. It is apparent that the methods being used for demonstrating the L.E. phenomenon in peripheral blood must be reevaluated in the light of newer developments and more certain techniques. On looking through the literature recently, in an attempt to find

whether or not there was a reversal of the L.E. phenomenon in the case of subacute or acute disseminated lupus erythematosus which undergoes remission with corticotropin or cortisone treatment, I found that reversal does not take place except temporarily in some cases.

DR. LESLIE P. BARKER: I have seen this patient on many occasions with Dr. Baker. She initially had discoid lupus erythematosus; that became disseminated; then she began to have febrile attacks accompanied by joint pains. A leucopenia developed with relative lymphocytosis, a sedimentation rate of 60, and low serum protein. Unfortunately, the resident did not include these findings on the chart. Recently L.E. cells were demonstrated in the peripheral blood.

The febrile attack and joint pains subsided. Her blood picture has returned to normal except for a persistently high sedimentation rate. Today she has the clinical picture of subacute disseminated lupus erythematosus, but with the previous blood picture, the lupus erythematosus should be classified as an acute disseminated type in the quiescent stage.

DR. SAMUEL IRGANG: Dr. Barker, would you say that she had the acute disseminated type of lupus erythematosus? At present, the patient does not present the symptoms to support that diagnosis.

DR. JOHN GROOPMAN: There was something mentioned there about the artichoke. I should like to have that explained.

DR. MABEL G. SILVERBERG: I would like to ask of persons who have treated more of these cases something about the handling of a case like this. This girl, in spite of the laboratory test, looks pretty sick to me today. Does one allow a patient like this to go around and follow her normal activity?

DR. LESLIE P. BARKER: I suggested using desiccated artichoke tablets because a physician friend of mine had had real improvement in two cases of discoid lupus erythematosus with this therapy. It did no good in this patient.

In answer to Dr. Irgang, I see no reason to keep this patient in bed so long as she is afebrile and in a remission.

DR. MARION B. SULZBERGER: May I ask a question? Why does not one use the name "subacute disseminated lupus erythematosus" for this case? It seems to me that this patient is now presenting the features that we connect with the subacute cases which have their ups and downs and combine or alternate certain features of the discoid type and other features of the acute disseminate type of lupus erythematosus.

DR. CHARLES WOLF: The point that should be emphasized is the fact that this case started as discoid lupus erythematosus, and has now become a subacute lupus erythematosus. It has a virulent appearance. The patient, although feeling well, looks from the clinical aspect quite ill. She has an angry-looking eruption covering the entire facies and disseminated lesions over her body. I would suggest, since it is a discoid type and cortisone has not been very responsive in effecting an improvement, the use of quinacrine (Atabrine) hydrochloride.

DR. VALENTINE C. BAKER: I always had a feeling that this was a case of acute lupus erythematosus. The girl has always shown symptoms of being right on the edge of being very ill. At times she will have pains in her joints and the eruption will become worse and she will be very sick. She does respond to cortisone therapy. She had cortisone only about three or four days, and she got at least a 45% improvement, but we do not like to increase the dose of cortisone and get her sick from medication in restraining the progress of the disease.

Case for Diagnosis: Actinomycosis with Superimposed Dermatitis Factitia? Actinomycosis (Arrested Case)? Dermatitis Factitia? Presented by DR. THOMAS N. GRAHAM.

Amyloidosis Cutis Improved by Occlusive Dressing. Presented by DR. JUAN LARRALDE.

Amyloidosis Cutis. Presented by DR. JUAN LARRALDE.

Ulcerative Sarcoid (Simulating Papulonecrotic Tuberculid). Presented by DR. S. IRGANG.

Rosacea? Presented by DR. E. LADANY and (by invitation) DR. P. MICHAELIDES.

Rosacea-like Tuberculid of Lewandowsky and Lutz. Presented by DR. LESLIE P. BARKER for DR. ALEX W. YOUNG.

Psoriasis? Presented by DR. ORLANDO CANIZARES and (by invitation) DR. J. DWINELLE.

Lupus Erythematosus, Chronic, Discoid: Face and Scalp. Lichen Planus: Legs, Thighs and Arms. Anetoderma (Schweninger-Buzzi Type): Back, Chest, Arms. Presented by DR. ALFRED ELIASSOW.

Lichen Nitidus (Tuberculous Causation?). Presented by DR. S. IRGANG.

Pemphigus Vulgaris. Presented by DR. ORLANDO CANIZARES and (by invitation) DR. H. SHATIN.

Marion B. Sulzberger, M.D., *Chairman*

J. Lowry Miller, M.D., *Secretary*

May 5, 1953

Parapsoriasis "En Plaque." Presented by A. C. CIPOLLARO for DR. J. ANDREI (by invitation).

L. Z., a white man aged 56, was first seen at the New York Polyclinic Skin Clinic on Feb. 24, 1953. His complaint concerned a chronic generalized dermatosis which had started 18 to 20 years previously as a pruritic, erythematous, round, pigmented plaque on the lower right side of his trunk. The itch would disappear for long or short periods, but would often recur, particularly after his not infrequent drinking and eating excesses. The eruption gradually spread from the original starting point to the rest of the trunk and to the extremities.

The patient, who has been a bartender, or waiter all his working life, is married and has a grown, healthy daughter. He denies having had any other cutaneous or atopic manifestations or any serious systemic affection.

He was treated with no avail by several general practitioners and dermatologists.

The patient presents several round or irregular, erythematous or yellowish-brown, furfuraceous plaques, which become confluent in the lower abdomen and lower back. When inspected closer, these lesions appear to be, especially in the zones of coalescence, finely reticulated. The stretching of the skin will make the net-like pattern even more evident.

Some discrete, smaller, round pigmented lesions involve the distal regions of the extremities but not the palms, soles, face, or scalp.

The scales are thin, parchment-like and more often than not, when removed, come off in rectangular lamellae, leaving an erythematous shiny base.

On both sides of the neck, especially on the right side, there are poikiloderma-like changes, with microtelangiectasias and pigmented spots, but very little evidence of atrophy. The onset of this cervical disturbance could not be determined.

A pathological specimen was submitted to Dr. Perry Sachs., whose histopathological interpretation follows:

"The superficial vessels are dilated and about them there is a mild focal reaction, composed of small round and wandering connective tissue cells. There is pronounced perivascular edema and some edema throughout the upper cutis. The epidermis is thin, dry, and shows no significant changes. However, in one area there is some edema and inflammatory cells within the epidermis. Overlying this area there is parakeratosis. While this is possibly parapsoriasis, a toxic erythema multiforme must be considered."

For therapy, soothing and keratolytic ointments were used locally.

Calciferol, a 50,000-unit capsule three times a day orally, was started only a few days ago.

DISCUSSION

DR. JOHN RUPPE JR.: My only comment is that here is a case of parapsoriasis "en plaque" of 20 years' duration and there are no changes suggestive of mycosis fungoides.

DR. H. WECHSLER: I should like to ask the discussers about their experience with calciferol in parapsoriasis and what results they have had?

DR. SULZBERGER: Who will answer that question?

DR. CONSTANCE MILLETTE BUNCKE: I would say this is a case of parapsoriasis that is very resistant to any therapy as opposed to the guttate type, which responds to calciferol, and especially to ultraviolet ray.

DR. ORLANDO CANIZARES: I agree with what Dr. Buncke said.

DR. J. ANDREI: This case was presented mainly because it started with itching, a symptom which was considered to be rare in cases of parapsoriasis. When Brocq, 50 years ago, submitted the present classification of this group of maculosquamous dermatoses, he emphasized that one of the cardinal points for diagnosis was the absence of subjective sensations, including pruritus. However, we are now becoming aware that the basic concepts in the interpretation

of parapsoriasis are changing. Pruritus now is considered quite a common denominator in many cases. Lapière (Liège, Belgium) in a large series of cases showed that fully 50% of his patients presented the symptom of itching.

The onset of the disease in our patient was ushered in, 20 years ago, by a round itchy plaque on the right side of the trunk. The sensation of itching eventually disappeared, but it frequently recurred, especially after drinking and eating excesses. An additional reason for presenting this case was the presence of poikilodermatous changes on the sides of the neck, which may be the precursors of mycosis fungoides.

Werner's Syndrome. Dr. A. Brodey and (by invitation) Dr. John Ruppe Jr.

S. S., a woman aged 28 years (Puerto Rican) showed generalized underdevelopment with skin changes on face and extremities. The patient said that ever since adolescence she has

Differential Diagnosis *

Symptoms	Werner's	Rothmund's	Progeria of Children with Nanism	Myotonic Dystrophy	Patient S. S.
Heredofamilial occurrence	3	2	0	2	1 ("Father was skinny like me")
Age of onset	20-30 yr.	3-4 mo.	2-5 mo.	20-30 yr.	23 yr.
Skin changes	4	4	4	1	4
Tightly drawn	4	0	1	1	4
Atrophic skin	4	2	2	2	4
Teleangiectasis	1	4 (at 3 mo.)	0	0	1
Scaling	2	4	1	0	0
Pigmentation and depigmentation	1	3	1	1	2
Ulcers	4	0	0	0	3
Canities of scalp hair	4	±	4	3	0
Muscle atrophy on distal parts	3	±	3	3	3
Atrophy of subcutaneous tissue	3	±	3	3	3
Diffuse arterial sclerosis	3	±	4	2	0
Bilateral cataract	4 (20-30 yr.)	4 (3-4 yr.)	0	3 (20-30 yr.)	0
Osteoporosis	3	0	2	1	1
Joint deformity	3	1	3	1	0
Proptosis	3	0	4	0	0
Sexual underdevelopment	4	2	3	3	3

Graded 1-4 according to severity

* Thannhauser, S. J.: Ann. Int. Med. **23:** 559, 1945.

always been "skinny" and that she has never had a menstrual period. About five years ago after a traumatic injury to her left ankle, a painful and slow-healing ulcer developed. Subsequently she had other similar ulcers on her ankle from time to time. For the last several months walking has been difficult and painful because of several calluses on the bottoms of both feet.

Her father died 23 years ago, and "was supposed to be skinny like me." Mother and six brothers are living and normally developed. No history of syphilis was obtained.

On physical examination the weight was 61 lb. (27.7 kg.), height, 57 in. (144.7 cm.), and B.P., 110/70.

Upon general examination the marked underdevelopment of the patient and the senile facies are apparent. There is a generalized loss of subcutaneous tissue and decrease in muscular substance. In the face this is manifested by a thinness of the nose with deep wrinkling and exaggeration of the normal skin folds, especially about the mouth. The skin changes are most marked over the lower legs. The skin there is tight, shiny, and atrophic, and the color of the toes is a dusky red. On the internal malleolus of the left ankle and also on the anterior

aspect of the ankle there are depressed and depigmented scars 3 cm. in diameter, surrounded by a pigmented border. On the left lateral malleolus there is a heaped-up keratotic lesion 1.5 cm. in diameter. On the soles of both feet there are hypertrophic keratotic lesions at the points of contact. All the toenails are thickened. The scalp hair appears normal, but hair in all other areas is scanty to absent. The breasts are completely undeveloped. No canities is present.

Examination of the heart, lungs, eyes, and other systems is normal. The patient is alert and clinically appears to be of normal intelligence.

Laboratory report: Urinalysis, no abnormal findings; red blood cell count, 4,000,000; hemoglobin content, 13.6 gm. per 100 cc.; white blood cell count, 12,000, with a differential distribution of 62% polymorphonuclear leucocytes, 28% lymphocytes, 3% eosinophiles, and 7% mononuclears; fasting blood sugar, 106 mg. per 100 cc.; Wassermann reaction, negative.

X-rays show several areas, rather ill defined, of decreased bony density in the shaft of the left tibia and fibula. There is no evidence of calcification in the vessels of the radiographed areas.

DISCUSSION

DR. G. KIOURTSIS: I have been studying Thannhauser's description of several cases of Werner's syndrome, which he distinguished from Rothmund's syndrome. I think that the following facts are of interest as far as both syndromes are concerned:

Werner's syndrome, which is a heredofamiliar disorder, has a tendency to occur in brothers and sisters. Rothmund's syndrome is also a recessive hereditary disturbance and usually begins in early childhood. In both syndromes there is a stunting of growth, but the changes in the musculocutaneous structure are not so marked in Rothmund's syndrome as they appear to be in Werner's syndrome. Furthermore, in Werner's syndrome there is premature loss of hair, hypogonadism, osteoporosis, and calcification of the blood vessels. There is a tendency to diabetes, and to the development of ulcers, especially in the lower extremities where pressure is exerted.

In both syndromes, cataracts occur, but sexual development is usually normal in Rothmund's syndrome, and osteoporosis is not observed. In Rothmund's syndrome ulcerative processes do not develop.

The cutaneous lesions in Werner's syndrome are seen in the calves, the feet, and to a slighter degree on the upper extremities and face, whereas in Rothmund's syndrome the lesions appear on the face, ears, and gluteal areas and later, on the extensor surfaces of the extremities.

In both syndromes there are trophic changes, but telangiectasia is characteristic of Rothmund's syndrome.

The sclerotic process is more pronounced in Werner's syndrome; however, the histopathology is not that of scleroderma.

DR. JOHN RUPPE JR.: For a complete clearcut diagnosis of Werner's syndrome this case lacks cataracts and canities. Cataracts may yet develop, as they usually come on at from 20 to 30 years of age, and the patient is 28 now. However, inasmuch as this is thought to be due to a hereditary recessive defect in the germ plasm, and her father is the only member of the family with a similar history, it is perfectly possible that all of the manifestations of the syndrome may not develop. Thannhauser also has noted incomplete cases.

Lymphocytic Infiltration of the Skin. Presented by DR. PAUL O. SHACKELFORD.

L. B., Jewish man, aged 32, complained of "rash on cheek and nose." This 32-year-old man lived in Palestine from 1935 to 1947. The eruption on the face began in 1946. Examination of the skin and inner organs for tuberculosis was performed and no evidence of this disease was found.

Shortly after arriving in the United States in 1947, this man sought medical aid. Lupus erythematosus was the diagnosis considered by the attending physician, and consequently the patient received 20 injections I.V. of gold sodium thiosulfate. This therapy had no effect on the course of the disease.

Since the onset (1946) there has been rather progressive involvement of the eruption, which has been characterized by remissions and exacerbations. The longest period of remission has been for an interval of two weeks. The course of appearance is not affected by season or sunlight. However, exposure at sea resulted in marked exacerbation on one occasion.

On the malar areas and forehead are discrete, elevated, papulonodular, and rose-bud lesions. These tend to coalesce to form infiltrated plaques measuring 1.5 to 2 cm. in diameter. Other single lesions are annular and circinate infiltrated lesions with a tendency to clear in the center.

Close examination reveals no dilatation of the follicles, no follicular plugging, no atrophy, telangiectasis, or scarring.

Laboratory Examinations: Urine porphyrin, negative on two occasions; white blood cells count, 7,400, with 62% neutrophiles, 1% eosinophiles, and 37% lymphocytes; hemoglobin, 17.3 gm. per 100 cc.; urine analysis, negative.

Sections of skin from the face revealed a relatively narrow epidermis without a rete pattern. No hyperkeratosis or follicular plugging was noted. The basal layer of the epidermis was normal. In the cutis one saw a striking infiltration of small lymphocytes, concentrated around blood vessels. This infiltration extended down to the subcutaneous fat. Longitudinal sections of blood vessels revealed a wide mantle of these cells. No germinal centers or germinal center-like formations are demonstrable in these masses.

This case, both clinically and histologically, is identical with a series of cases presented by Dr. Max Jessner in a paper read at the Bronx Dermatological Society.

DISCUSSION

DR. ROBERT CLARK: I had the privilege of seeing this patient shortly after hearing Dr. Jessner's paper at the Bronx Dermatological Society meeting, and I think this very well fits in with the lymphocytic infiltration of the skin. I do not think it is necessary to name a new entity, but it is important for the exclusion of more serious disease such as lupus erythematosus. I know of one particular case that was surveyed out of the Coast Guard with the diagnosis of lupus erythematosus. We were sure it was that, except that the biopsy was not typical of lupus. As I look back at that now, it seems possible that it may very well have been lymphocytic infiltration of the skin.

DR. HERBERT J. SPOOR: The lesion superior to the right brow seemed to differ quite a little bit from the lesions on the malar process. I thought that this was rather typical clinically of a lupus erythematosus lesion. I should like to see another biopsy.

DR. D. G. BROOKING: I have a patient with lesions, very similar to this at New York Hospital, which we thought at first to be lupus erythematosus. She responded well to small doses of x-rays. However, on cessation of therapy the lesions recurred on the original sites.

DR. PAUL O. SHACKELFORD: Cases similar to this probably have been overlooked in the past. If we look for them more closely in the future, we shall probably find more of them.

Infection of the Pubic Region with Microsporum Audouini. Presented by DR. G. SILVERBERG and DR. BERNARD J. OSEROFF.

D. M., a girl aged 17, was first seen at this clinic on March 17, 1953, for a condition of three months' duration which had been unsuccessfully treated with various ointments.

The patient's 10-year-old brother had been seen at this clinic two months previously on Jan. 5, for tinea capitis of the occipital area. Microsporum audouini was obtained on culture and the affected area showed fluorescence under Wood's light. The eruption continued to spread despite repeated manual epilation and topical application of 5% ammoniated mercury ointment. Roentgen ray epilation on Feb. 13, 1953, had produced apparent cure. The child is still under observation. The patient's mother and another brother, aged 24, are free of infection.

She presented circinate lesions with erythematous raised borders and scaly centers involving the pubic area and the lower abdomen. There was some spread toward the right inguinal region, and a circinate lesion was seen in the left lower lumbar area. The scalp and axillae were free of involvement.

Wood's light examination revealed bright green fluorescence of the pubic hair. Hairs from the pubic region showed on direct microscopic examination a typical ectothrix spore sheath as well as extensive intrapilary involvement. Scales showed numerous filaments. Microsporum audouini was cultured from both hairs and scales on Sabouraud's glucose agar and rice medium.

DISCUSSION

DR. BERNARD J. OSEROFF: We presented this patient tonight because of the rarity of her condition, i. e., Audouini infection of the pubic area. There have been reported Audouini infections of the scalp and eyebrows, but so far as we could find there was no report of Audouini infection of the pubic area.

DR. HERBERT J. SPOOR: I do not claim credit for being much of a mycologist, but I think the impressive point here is that the girl is 17 and that she does have an Audouini infection in the pubic area, when infection with such an organism would be unlikely in a girl of 17, even on the head. Now I am enough of a mycologist to want to compare the organism on the boy with that on the girl. I think there are sufficient variations within the species that one could do that microscopically or possibly on culture, and if one could prove that this organism was the same one as that which came from the child that absolutely would prove the case for transfer of infection.

DR. MARION B. SULZBERGER: I should like to ask the members if they have ever seen such a case or know of a report of such a case. I have never seen one and I have never heard of one.

DR. JOSEPH G. SILVERBERG: As to the therapy, we intend to continue with manual epilation and topical fungicides. Since the disease is self-limited, we consider radiation therapy, with its possible sequelae, unwarranted.

Comparison of the infecting organisms in the brother with that in the girl is impossible because the boy has been epilated and cured. In conclusion, may I add that in all the literature available on Microsporum audouini infections of hair, it has been reported involving the scalp, eyebrows, eyelashes, and axilla, but never, to my knowledge, the pubic region.

Presented for Diagnosis: (a) Pyoderma-Intrauterine Infection, (b) Epidermolysis Bullosa, (c) Pemphigus Neonaturum. Presented by DR. JEAN A. CRAMER.

Pemphigus Foliaceus (Senear-Usher?). Presented by DR. WALTER J. SCHMIDT.

Erythroderma Psoriaticum. Presented by DR. S. PECK for DR. G. KIOURTSIS.

1. Tuberculosis of the Skin: (a) Papulonecrotic Tuberculid, (b) Erythema Induratum, (c) Micropapular Tuberculid (Including Rosacea-Like Tuberculid), (d) Tuberculosis Lichenoides. 2. Tuberculosis Lymphadenitis. 3. Biologic False Positive Serologic Tests for Syphilis. 4. Polyarthritis of Unknown Cause. Presented by DR. MARVIN BRODEY.

Congenital Lymphagiectasia. Presented by DR. CONSTANCE MILLETTE BUNCKE.

Pemphigoid Eruption of the Senear-Usher Variety. Presented by DR EUGENE TRAUGOTT BERNSTEIN for DR. LAWRENCE J. KELLY.

Fibromyoma (Leiomyoma Cutis). Presented by DR. BEDFORD SHELMIRE JR.

Lepromatous Leprosy. Presented by DR. ROGACHEFSKY.

Familial or Hereditary Hemorrhagic Telangiectasia. Presented by DR. D. G. BROOKING.

Case for Diagnosis. Granuloma Annulare (?) Granulomatosis Disciformis Chronica Et Progressiva (Miescher) (?). Presented by DR. ROYAL G. JENNINGS

Epidermolysis Bullosa, Dystrophic Type. Presented by DR. HERBERT J. SPOOR.

Lichen Striatus. Presented by DR. E. LADANY for DR. J. ANDREI (by invitation).

Lichen Nitidus. Presented by DR. A. Montgomery and (by invitation) DR. J. RUPPE JR.

Lupus Vulgaris—Generalized Lymphadenopathy—Pulmonary Tuberculosis with Bilateral Pleural Effusions. Presented by DR. S. PECK for DR. G. KIOURTSIS.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Fred D. Weidman, M.D., *Chairman*

Bertram Shaffer, M.D., *Secretary*

May 15, 1953

Acrosclerosis and Scleroderma. Presented by DR. CARROLL S. WRIGHT, DR. REUBEN FRIEDMAN, and DR. JACK WEINER.

H. H., a white man aged 51 years, stated that he became ill in 1949. About 18 months ago his fingers and toes became puffy and later the skin became tight, so that by August, 1950, he was unable to close his hands. Later his knees and hips became stiff. He developed pains in the chest and complained that in winter his fingers turned pale and ached on exposure to cold.

On Jan. 23, 1950, he was treated with cortisone and later with sex hormone and corticotropin (ACTH), without improvement. He subsequently complained of "stomach trouble" in the form of substernal burning, difficulty in swallowing, and the spitting up of "dark, jelly-like material." Roentgenographic studies of the gastrointestinal tract and the chest were reported negative.

The patient was a middle-aged white man not appearing acutely ill. He had difficulty in arising from a sitting position, and his gait was slow and somewhat guarded. The skin of the face was brown and taut. The nose appeared sharp, with the skin drawn tightly over the cartilage. The lips were thin and radially furrowed. The mouth was edentulous. The skin of the neck, clavicular region, and upper chest was somewhat sclerotic, and it was difficult to raise the skin from the underlying tissue. The fingers were stiff and slightly flexed and manifested a board-like induration. The induration extended up the forearms, becoming less severe, so that the skin above the elbows was comparatively normal in appearance and on palpation. The toes and lower parts of the legs showed similar, but less severe, changes.

On Sept. 24, 1951, acetylsalicylic acid (Aspirin), 0.3 gm., four times daily, and potassium paraaminobenzoic acid, 20 cc. of a 10% solution six times a day, were given. At first there was little improvement, but by Nov. 15, 1951, both the skin and the arthritic manifestations appeared better. On Dec. 21, the patient complained of eructations and vomited small clots of blood. Roentgenographic studies showed some functional impairment of the esophagus—"presence of feeble and ineffective esophageal peristalsis in the prone position." Clinically, it was judged that there was probably esophagitis secondary to diffuse sclerosis.

Since then there has been progressive improvement, including a gain in weight, diminished arthritic symptoms, more flexible skin, and lessened gastrointestinal disturbances. He recently had an episode of bloody diarrhea, apparently a form of infectious gastroenteritis. On May 9, 1953, he noted pain and limitation of motion of his left arm, especially flexion.

A dynamic traction splint has been constructed to aid the return of finger movements.

Dermatitis Herpetiformis Treated With Paraaminobenzoic Acid. Presented by DR. CHRIS ZARAFONETIS (by invitation).

N. L., a white woman aged 57 years, in April, 1950, developed a generalized polymorphic eruption. This was composed of discrete and grouped vesicles and bullae which later formed crusted and eroded lesions, pigmented areas, and some scars. It involved chiefly the face, neck, sternal and interscapular areas, the sacrum, and the extremities and was associated with severe pruritus, especially marked at night.

Under the diagnosis of dermatitis herpetiformis, treatment was started with sulfapyridine and tripelennamine (Pyribenzamine). There was spectacular improvement, but treatment was stopped in September, 1950, because agranulocytosis developed (leucocytes, 950 per cubic millimeter). Within two weeks the eruption recurred. A trial of sulfadiazine was started, but the leucocyte count fell. Penicillin oxytetracycline (Terramycin), vitamin B_{12}, nicotinic acid (niacin), tripelennamine, and progesterone did not improve the eruption. Potassium arsenite (Fowler's) solution produced equivocal effects. On Aug. 22, 1951, treatment with potassium paraaminobenzoate (KPAB), 3 gm. six times a day (30 cc. of a 10% solution) was begun. A flare-up of the skin lesions occurred in the first few days, but by Aug. 29, 1951, there was beginning improvement (no new lesions and some drying of the old ones). Occasional mild exacerbations of the skin lesions have occurred, and at times as much as 24 gm. of KPAB has been given.

DISCUSSION

DR. CHRIS ZARAFONETIS (by invitation). Once we get the skin softening in scleroderma, we can use splints and physical therapy and obtain results which we have been unable to obtain on drug therapy alone. Our best results have been in patients who have been on PABA treatment for more than six months.

The scleroderma patient has gained over 20 lbs. (9.1 kg.).

DR. BENJAMIN GROSS: Has Dr. Zarafonetis used PABA in lupus erythematosus? We treated three patients with this drug, but all became very sick. Even on very small doses they lost weight.

DR. CHRIS ZARAFONETIS (by invitation): Had they previously had heavy metal?

DR. BENJAMIN GROSS: One patient with lupus erythematosus had had bismuth.

DR. CHRIS ZARAFONETIS (by invitation): Of all the groups we have treated, we find the lupus erythematosus group has the most difficulty in tolerating PABA. But the thing that has interested me most of all is that patients with lupus erythematosus arthritis, dermatitis herpetiformis, or lymphoblastoma who have previously had heavy metal therapy, when started on PABA almost invariably have a flare-up of their disease, with fever and gastrointestinal upsets. People who have not had heavy metal do not have this type of reaction. One of our arthritics who had had a gold eruption, when we started PABA years later, had a flare-up immediately at the site of the previous gold dermatitis. I point that out mainly to show that PABA may actually provoke a release mechanism for previously administered heavy metal. We give PABA in the 10% solution. We find patients cannot tolerate as large a dose in tablet form.

We have treated 400 patients with PABA and have observed some leucopenia (counts in the neighborhood of 3,000 to 3,200). We have not stopped treatment because of this. PABA is an amino acid; it is in every food, and I should be surprised if it produced agranulocytosis.

Lichen Sclerosus et Atrophicus (May, 1952). Morphea? Presented by DR. CARROLL S. WRIGHT.

C. S., a white girl, aged 13, seen only once, in May, 1952. There was a history of a spreading white patch on the chin of two years' duration. There was no history of trauma. On May 23, 1952, there were atrophic white patches involving the right side of the chin and appearing slightly on the neck in the region of the ears. There was hemiatrophy of the tongue.

The patient was treated with bismuth sodium triglycollamate (Histrimate) tablets, one three times a day.

DISCUSSION

DR. BERTRAM SHAFFER: I should like to suggest that this might be an example of linear scleroderma. The tongue was atrophic on the right side and, of course, hemiatrophy in association with linear scleroderma is not unknown. That would strengthen the idea that this is possibly a case of linear scleroderma rather than lichen sclerosus. Another point I would emphasize in favor of scleroderma is the hard, board-like, indurated, and deeply adherent linear depression created by this condition. I have not seen lichen sclerosus et atrophicus cause deep hardening and deep depression of the tissues such as this case presents.

DR. ALBERT M. KLIGMAN: I think it worth emphasizing again that the distinction between these two entities may be artificial; these may, in fact, be the same disease. Cases have been observed in which, histologically, the condition has progressed from one to the other in the same patient.

DR. CARROLL S. WRIGHT: I saw this case once a year ago, and I will agree with Dr. Kligman that it has changed considerably. I think the atrophy is much more marked than it was a year ago. I wanted to do a biopsy when I saw the patient before, but the parents refused.

Rosacea with Hypertrophic Changes Predominantly Involving the Cheeks. Presented by DR. JOHN F. WILSON.

H. F., a white man aged 43 years, presented over both cheeks, ears, and nose lobulated hypertrophic masses with conspicuous glandular openings and telangiectatic blood vessels. The tissue was red and purplish and covered with superficial pustules. There were also comedones, papules, and pustules on the chest and back.

About six years ago his face became red and pustules appeared. He also noticed a diminution of his hearing. An otolaryngologist opined that the deafness was the result of swelling of the ear canals.

The report on the biopsy specimen (Dr. J. Butcher) was as follows: "The tissue was partially bordered by an irregular layer of stratified squamous epithelium. Superficially there was a thin layer of hyperkeratin. Within the corium and associated around the hair shaft was a fairly well demarcated zone consisting predominantly of lymphocytes, plasma cells, and an occasional eosinophile. The histologic features were compatible with the gross diagnosis of rosacea."

Preliminary rosacea therapy has been carried out preoperatively.

DISCUSSION

DR. HERBERT M. LEAVITT (Easton): That patient has difficulty in hearing. Are there hypertrophic changes in the ear canals similar to those on the cheeks?

DR. JOHN F. WILSON: This patient has had difficulty in hearing since he first developed changes on the cheeks. His hearing improved when the swelling in the ear canals subsided. He has not had a recent otitic examination. I understand that cases of hypertrophic rosacea have been reported on the cheeks of German war prisoners after World War I, who had been prisoners in Russia and exposed to cold.

DR. HERMAN BEERMAN: Some of you recall Dr. Abbey's cases, which seem similar to the present one. The sections showed nothing but sebaceous gland hyperplasia, and as I recall it, the process was called cutis verticis gyrata of the face.

DR. IRA L. SCHAMBERG: Would Dr. Wilson describe the surgical procedure he is contemplating?

DR. JOHN F. WILSON: I plan to remove the hypertrophic areas by using electrosurgery, destroying small areas at a time until I reach a fairly normal configuration of the face. Certainly the hypertrophy is beyond what is usually seen in rhinophyma, and surgically it will be a difficult problem.

DR. MEYER L. NIEDELMAN: Is Dr. Wilson going to use the multipolar cutting current?

DR. JOHN F. WILSON: The bipolar.

DR. MEYER L. NIEDELMAN: I favor the unipolar cutting current. It results in less bleeding, the tissue removal can be better controlled, and the scarring is less. A cold pack and the use of epinephrine (Adrenalin), 1 oz. (28.35 gm.) to the pint, will also help to minimize the bleeding.

Lichen Planus. Presented by CAPTAIN W. N. NEW, (MC) USN.
Sarcoidosis. Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. DONALD N. TSCHAN.
Chronic Discoid Lupus Erythematosus? Urticaria Pigmentosa? Adenoma Sebaceum? Presented by DR. JOHN M. SIEGEL, Allentown, Pa.
Melanosis of Riehl. Presented by DR. JOSEPH V. KLAUDER.
Lichen Sclerosis et Atrophicus. Presented by DR. JOHN P. SCULLY, Reading, Pa.
Reticulum-Cell Sarcoma. Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. CHRIS ZARAFONETIS.
Dermal, Junction, and Compound Nevi. Presented by DR. CARROLL F. BURGOON JR.
Chronic Discoid Lupus Erythematosus. Presented by DR. MEYER L. NIEDELMAN and DR. ADOLPH BLEIER and (by invitation) DR. JOHN H. YEAMAN.
Discoid Lupus Erythematosus. Presented by DR. MEYER L. NIEDELMAN.
Discoid Lupus Erythematosus. Presented by DR. MEYER L. NIEDELMAN.
Dermatitis Medicamentosa. Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. DONALD N. TSCHAN.
Colloid Milium? Presented by DR. CARROLL S. WRIGHT, DR. MEYER L. NIEDELMAN, DR. BYRON CLYMAN, and (by invitation) DR. D. N. TSCHAN.
Erythrodermic Congenitale Ichthyosiforme. Presented by DR. REUBEN FRIEDMAN.
Necrobiosis Lipoidica Diabeticorum. Presented by DR. CARROLL S. WRIGHT and DR. BRYON CLYMAN.
Rosacea-Like Tuberculid of Lewandowsky. Presented by DR. E. R. GROSS and (by invitation) DR. D. N. TSCHAN.
Photosensitive Dermatitis Resembling Prurigo Aestivalis of Face. Sensitivity to Neomycin-Gramicidin (Spectrocin?). Recurrent Fixed Eruption of Forehead and Face Due to? Presented by DR. REUBEN FRIEDMAN.
Parapsoriasis (Lichenoides Chronica with Some Varioliform Lesions). Presented by DR. JOHN B. ROXBY JR.
Sulzberger-Garbe Disease. Seborrheic Dermatitis. Presented by DR. REUBEN FRIEDMAN.
Exudative Discoid and Lichenoid Chronic Dermatosis of Sulzberger-Garbe. Presented by DR. REUBEN FRIEDMAN.
Gumma of the Septum and Palate. Presented by DR. MEYER L. NIEDELMAN.
Acute Psoriasis Relieved by Vitamin A(?). Presented by DR. REUBEN FRIEDMAN.

SAN FRANCISCO DERMATOLOGICAL SOCIETY

Edward Levin, M.D., President

Max E. Krause, M.D., Secretary

Oct. 17, 1952

Case for Diagnosis—(Glossitis Rhombica Mediana?). Presented by DR. H. V. ALLINGTON and DR. R. R. ALLINGTON, Oakland, Calif.

Mrs. L. C., aged 26, has had a lesion on her tongue for approximately 18 months. It was first called to her attention by her dentist. It has always been asymptomatic. There is no history of injury. She had taken no medication prior to onset. She had sucked a penicillin lozenge for a sore throat shortly before we first saw her on April 6, 1951, but had not done so prior to onset.

The lesion was present in approximately the center of the dorsal surface of the tongue and measured about 0.75 by 3 cm. in diameter. It consisted of a slightly reddened area of superficial maceration and loss of papillae. There was moderate infiltration, particularly about the margin. There was no ulceration, and the lesion was not tender. No regional adenopathy was noted.

A blood Kahn test was negative, and the lesion seemed to be less marked after two weeks of isotonic sodium chloride solution mouth washes.

She was not seen again until May 9, 1952, over a year later. The lesion appeared essentially the same. A punch biopsy was done at that time, and the section is presented. No treatment has been given.

Microscopically there is a marked and fairly uniform acanthosis. The epidermal cells are large and a fair number of mitoses are present, but there is no disorder and the basal layer is intact. There are areas of intercellular edema and inflammatory cell infiltration in the epidermis. Several intraepidermal microabscesses are present. The dermis shows an intense chronic inflammatory reaction, with a large number of new blood vessels, round cells, polymorphonuclear leucocytes, some plasma cells, and large connective tissue cells.

We believe that the process appears to be one of chronic inflammation rather than a neoplasm.

The location, the lack of symptoms, and the chronicity suggest the diagnosis of glossitis rhombica mediana. The character and intensity of the inflammatory reaction may be unusual for this condition.

DISCUSSION

DR. H. ALLINGTON, Oakland, Calif.: I had hoped that we might have had more discussion regarding the diagnosis. I wondered what the experience of the others is—whether we should let things slide along since the patient is not bothered or whether treatment of some active sort is definitely indicated.

Localized Myxedema. Presented by DR. ALBERT SHUMATE.

M. F., a 44-year-old white woman, was first seen two weeks ago with a history of swellings appearing in both lower legs shortly after a thyroidectomy 18 months previously.

Physical examination reveals boggy purplish swellings in both anterior lower legs. A marked exophthalmos, also of recent origin, is present. The basal metabolic rate was reported as normal.

Histopathological examination discloses findings typical of localized myxedema.

DISCUSSION

DR. EUGENE FARBER: We have been given a supply of intravenously administered trypsin for experimental use, and in the protocol which comes with this new method of administering trypsin it is stated that albumin and globulin and mucinous substances will be absorbed in the tissues. If the presenter would like a supply of this, it is entirely safe so far as its administration is concerned. It is given intravenously with saline and 250 triptar units run in a period of two and a half hours; the treatment should be given daily for about four or five infusions.

DR. PAUL CROSSLAND: This is a typical case of localized pretibial myxedema associated with exophthalmos. The patient's history is interesting in that symptoms did not appear until six months after her thyroidectomy.

There is strong presumptive evidence that localized myxedema is etiologically unrelated to the constitutional myxedema of hypothyroidism. In fact, it is almost always associated with or preceded by clinical manifestations of diffuse toxic goiter and is usually initiated by thyroidectomy.

Observations by Dr. Curtis and others (ARCH. DERMAT. & SYPH. **60**:318-337 [Sept.] 1949) support the hypothesis that localized myxedema and exophthalmos are probably related manifestations of the same underlying disorder. Experimental evidence suggests that a thyroid-stimulating hormone generated by the anterior lobe of the pituitary gland is the major cause of progressive exophthalmos. In diffuse goiter the activity of this hormone is offset by increased production of thyroxin in the thyroid gland. When the thyroid gland is excised, most of the stimulating hormone continues to be active, causing actual increase in retrobulbar volume from edema and cellular infiltrate and in many cases concomitant localized myxedema.

Irradiation of the pituitary gland in treating localized myxedema is dangerous to the patient and of questionable benefit. Localized injection of hyaluronidase has reduced the size of the plaques in some cases, which is ascribed to hydrolysis, by this enzyme, of the hyaluronic acid contained in these lesions.

Case for Diagnosis: Lichen Planus? Presented by DR. JULIUS STONE (by invitation).

L. M., a 36-year-old Negro woman, entered Stanford service of San Francisco County Hospital April, 1952, with an eruption on her face and with ascites. The eruption had appeared six months previously as a pruritic dry macular lesion covered with a little scale over the right orbital ridge. This lesion gradually increased in size. Within the next two months a number of similar lesions appeared on the cheeks, bridge of the nose, and vermillion border of the lips. She applied an ointment to the lesions which was irritating and which resulted in weeping and crusting. Two months prior to entry her abdomen began to swell and became markedly distended. She had no systemic symptoms or signs, such as arthralgia, jaundice, fever, edema, or swelling of the parotid glands. She had been treated adequately for secondary syphilis four years ago. Examination of the skin revealed an ovoid lesion with an irregular raised red margin and a central depressed atrophic area bluish-black in color. There was little scaling of the surface and no excoriation. Similar lesions were present on the left side of the forehead near the hairline, the bridge of the nose, the cheeks, and the lips. There were several nontender shotty cervical lymph nodes. In addition, she had ascites with no visible collateral abdominal veins.

On laboratory study the serologic tests for syphilis were positive, with 32 and 64 dilution units. Blood studies revealed a corrected Wintrobe sedimentation rate of 41 mm. The white blood cell count was 6,500, with a normal differential distribution. Total protein and A/G ratio were normal. Liver function studies were normal. The Mantoux reaction was positive at a dilution of 1 to 1,000. No L. E. cells were found in the bone marrow. Examination of smears and culture of sputum and gastric washings were negative for acid-fast bacilli. A paracentesis was done, and examination of the fluid revealed a specific gravity of 1.022, with 98% lymphocytes and 2% polymorphonuclear leucocytes; culture of the fluid was negative for acid-fast bacilli. A chest x-ray showed an infiltration in the left upper lobe, which did not change on subsequent examination over the next three months.

A specimen taken from the forehead for biopsy was interpreted as lichen planus; a lymph node biopsy revealed a noncaseating granuloma.

The patient's course in the hospital was uneventful. She was discharged in June, at which time the face lesions were dry and the ascites had cleared.

One month after discharge, July, the patient came to Stanford outpatient skin clinic with large areas of crusted and secondarily infected dermatitis over her entire forehead, cheeks, chin, nose, and lips. In addition, lesions developed on her forearms, neck, and legs, consisting of papules and nodules of various sizes which were violaceous, flat-topped, discrete, and confluent, and covered with a slight scale. Secondary infection of the face lesions cleared slowly on treatment, leaving scaly dry crusted patches with a reddish-violet color. Flat-topped angular papules appeared on the left side of her face. Small pinpoint and stellate whitish papules were noted on the buccal mucosa and whitish patches on the inner surfaces of the labia majora.

Biopsy specimens taken from the right preauricular area, the left forearm, and the sternum were diagnosed as lichen planus. The patient was given intramuscular injections of bismuth subsalicylate in oil once a week.

DISCUSSION

DR. HERMAN ALLINGTON: I think that this is a very interesting and confusing case, and I am not at all certain what the basic problem is. I should like to agree that I believe the warty-papular element is probably one of lichen planus, and I think the lesions individually suggest, to some extent, there was evidence of Koebner's phenomenon in several groups of lesions, although perhaps not as clearly as we would like to see it, and I felt that the histopathologic picture was compatible with that diagnosis. I should like to suggest that lichen planus at times can be an opportunist disease and can engraft itself upon some other picture. I have recently seen one patient, a youngster about 14 or 15 years old, in whom I felt that the classic picture of an atopic eczema was present. This cleared to a large extent with time

and, to some extent, probably because of some treatment; as it cleared, engrafted in the areas where scratching was most marked, there developed again what I thought were lesions characteristic of lichen planus.

Congenital Syphilis with Periostitis and Delayed Herxheimer Reaction. Presented by DR. M. F. ALLENDE and DR. ELLA COLLIER (by invitation), Oakland, Calif.

J. S., an 11-year-old American Negro boy, noticed pain and swelling of the left shin on Aug. 25, 1952. He received two injections of penicillin and was given oxytetracycline (Terramycin) 0.4 gm. daily for three days. The pain became almost completely incapacitating, and he was hospitalized on Sept. 2.

History revealed that a serological examination had been performed on his mother prior to delivery and had been found to be negative. He is said to have had an eruption on his face and legs at the age of 5 days, but this disappeared spontaneously in three or four days. When the patient was age 8 months, another eruption appeared which lasted three days. His mother was found to have a positive serology in 1945 and received adequate treatment for syphilis. This was repeated twice more during subsequent pregnancies which ended by deliveries of normal children.

Physical examination reveals the following positive findings: (1) saber shins which were exquisitely tender on admission, (2) saddle nose, (3) prominent frontal bosses, (4) scaphoid shoulders, and (5) Hutchinson's teeth.

Laboratory examination: Blood serology: Kolmer 444,444; Kahn negative; Mazzini negative. Cerebrospinal fluid normal. Urine normal. White blood cell count 10,000, with normal differential distribution.

X-ray examination showed a bilateral tibial periostitis, with some involvement of the fibulae.

Penicillin therapy, 600,000 units daily for 14 days, was started again on Sept. 2.

The clinical improvement has been dramatic, in view of the marked disability which existed previous to hospitalization; however, x-ray examinations on Sept. 15 show a marked increase in periostitis bilaterally both on tibula and fibula, which could be interpreted as being a delayed Herxheimer reaction.

DISCUSSION

DR. M. E. ALLENDE: Most dermatosyphilologists of my generation are quite familiar with early syphilis as seen during the war, but are less acquainted with the late manifestations, particularly in the rarer forms, such as osseous involvement. For that reason, I felt it would be of interest to present this child with all the stigmata of congenital syphilis and an active bilateral fibroperiostitis. In addition, during the course of treatment, there appeared to be what might be interpreted as a delayed Herxheimer reaction. This was evidenced by the increase in the roentgenological abnormalities, as contrasted with the clinical improvement.

Parapsoriasis en Plaques (Brocq). Presented by CAPTAIN JOHN P. BRISKE (by invitation), Medical Corps, Letterman Army Hospital.

W. F., a 22-year-old soldier, was first seen in January, 1952, because of a nonpruritic eruption of recent onset. Examination disclosed a maculopapulosquamous eruption of the trunk and proximal portion of the extremities. There was a tendency for the oval plaques to be distributed with their long axes in the lines of cleavage. Results of serologic examinations were negative. The clinical impression at that time was pityriasis rosea, and ultraviolet light therapy was started. There was some improvement after six treatments, but it was not possible to follow the patient further at that time.

The patient was next seen in June, at which time he presented an extensive nonpruritic nonindurated maculopapulosquamous eruption of the entire body, except for the palms, soles, head, and face. The plaques were of irregular size and shape. The physical examination was otherwise normal. The results of routine laboratory studies, including roentgenographic examinations of the chest, blood cell counts, serologic examination, and urinalysis, were within normal limits. The results of repeated examinations and cultural studies for fungi were negative. Two specimens taken for punch biopsy revealed the histologic changes of a chronic nonspecific dermatitis. The clinical impression was parapsoriasis en plaques.

The patient received ultraviolet light therapy daily for about three weeks, with only slight improvement. He also received vitamin D, 100,000 to 150,000 units daily during a period of about two months. There has been only slight improvement since this therapy was begun.

DISCUSSION

DR. EDWARD RINGROSE: I agree with the diagnosis as presented. In looking at the patient today, I thought of mycosis fungoides or, possibly, psoriasis. I probably would have thought of pityriasis rosea when it was more limited in extent. I think the histopathological picture of a nonspecific chronic dermatitis with a scanty round-cell infiltrate in the upper cutis, chiefly perivascular; slight colliquative degeneration of the basal-cell layer; slight hyperkeratosis, and slight parakeratosis fits well the diagnosis as presented of parapsoriasis en plaques. It certainly rules out mycosis fungoides and psoriasis. So far as therapy goes, I suggest continuation of ultraviolet light, and, in conjunction with that, the use of coal tar solution, N. F., or some crude coal tar preparation the night before. I believe that in most cases of parapsoriasis of this type there is at least temporary response to such therapy.

Sarcoidosis. Presented by DR. M. F. ALLENDE and (by invitation) DR. ELLSWORTH DOUGHERTY and DR. S. OPPENHEIMER.

E. H., a 40-year-old American Negro woman, was first seen in July, 1952, because of cutaneous lesions on the face which had been present for several months. She had been treated for late syphilis in 1947, receiving 50 weekly injections in the hip. No spinal fluid examinations had been performed.

Physical examination shows the following abnormal findings: (*a*) circinate papules 0.5 to 1 cm. in diameter in both nasolabial folds, both buccal commissures, and near the right eye (*b*) blood pressure 186/100 and a soft systolic murmur at the base of the heart.

Laboratory examinations: Blood serology: Kolmer negative; Kahn 333; Kline positive; serum albumin 3.8 mg. per 100 cc.; serum globulin 3.2 mg. per 100 cc.; hemoglobin 12.1 gm. per 100 cc., white blood cell count 4,600, with normal differential distribution; urinalysis showed the presence of albumin; tuberculin test (OT 1 to 10,000) negative.

X-ray examination of the chest indicates the presence of enlarged hilar nodes, particularly on the right side.

Pathology examination of a biopsy specimen from the right nasolabial fold shows the presence of naked epithelioid tubercles, compatible with a diagnosis of sarcoidosis.

Treatment consisted of penicillin administration, 6,000,000 units over a period of 20 days, without change in the cutaneous lesions.

DISCUSSION

DR. R. ALLINGTON: Examining the patient and considering all the accompanying evidence, I can agree with the diagnosis. I think clinically, had I seen the patient, I would have considered syphilis as an initial diagnosis, taken blood for a Wassermann examination, given penicillin treatment, and would have been very surprised when the lesions did not disappear. I wonder in what order the diagnosis of sarcoidosis was made in this instance.

DR. ALLENDE: Most of us when first seeing this patient were guilty of making a hasty diagnosis, based on a positive serology with the presence of split papules at the corners of the mouth, and, therefore, started this patient on a course of penicillin therapy. A dark field examination had not been performed. Dr. James Bennett, however, had made a diagnosis of sarcoidosis on a clinical basis. This was confirmed by the lack of response to penicillin therapy, subsequent findings, such as a negative tuberculin test; the presence of hilar nodes, and, finally, the pathological changes found on the biopsy specimen.

In the last few months there have been a few reports in the literature on cortisone therapy for sarcoidosis—about 30 cases altogether, most of them with favorable results. I think that the use of cortisone in sarcoidosis is justified on several counts. This disease is not quite as benign as sometimes mentioned. It can become incapacitating, and the mortality rate is around 20%; also, its response to cortisone therapy is of importance from an etiologic and pathogenic viewpoint, particularly when contrasted with the bad effects of such treatment on tuberculosis. This contrast would tend to militate against a relationship between the two diseases. In the

cases so far reported, only one patient has gone on to develop frank tuberculosis. Many more patients with sarcoidosis are receiving cortisone therapy in other institutions, and I think that had some of them developed tuberculosis we would have heard more about it.

Now it is felt that Negroes with sarcoidosis are more likely to develop tuberculosis than white patients. For that reason, one might be tempted in this case to use streptomycin or *p*-amino-salicylic acid or isonicotinic acid in conjunction with cortisone. Of course, this would defeat the investigative approach to the problem, and, in view of the patient's good general status, a course of cortisone alone will be tried.

Urticaria Pigmentosa Beginning in Adult Life. Presented by DR. H. L. JOSEPH, Vallejo, Calif.

J. B., a 51-year-old machinist, has had a nonpruritic skin eruption on the trunk and the extremities since 1941. It began after the administration of "cold shots" and tablets which caused him to break out in "hives." The eruption was first noticed on the back and gradually spread to involve the remaining areas. He has been seen by several other dermatologists.

He had an operation for the removal of a thyroglossal duct cyst in 1917 and for a recurrence in 1923.

The lesions are discrete, 1 to 4 mm. purplish-brown macules and maculopapules. They are closely arranged over the entire trunk, with scattered lesions over the extremities, particularly on the flexoral surfaces. Dermographism is demonstrable.

The increased amount of melanin in the biopsy specimen is due to the fact that the patient had a deep sun tan when it was taken from the back.

DISCUSSION

DR. JOSEPH, Vallejo, Calif.: Other cases of urticaria pigmentosa have been reported after the administration of various types of vaccines and immunizing substances, including tetanus toxoid and influenza vaccine. I was unable to determine what this patient was given in 1941 at the onset of the eruption; however, several types of vaccine as prophylaxis against the common cold were in vogue at that time.

Morphea Guttata. Presented by DR. FRANCES A. TORREY; DR. S. WILLIAM LEVY (by invitation), and DR. FRANK K. HAIGHT.

Lupus Vulgaris. Presented by DR. WALTER E. WEBER.

Lymphocytoma Cutis or Spiegler Fendt Sarcoid. Presented by DR. B. F. RYAN.

Keratosis Follicularis. Presented by CAPTAIN JOHN P. BRISKE (by invitation).

Acrodermatitis Chronica Atrophicans. Presented by DR. KEMP H. DOWDY.

Generalized Exfoliative Dermatitis (Psoriasis?): Cortisone-Induced Cushing Syndrome. Presented by DR. KEMP H. DOWDY.

Lupus Erythematosus Chronic, Disseminated. Presented by DR. EUGENE FARBER.

Porokeratosis Mibelli. Presented by DR. FRANCES KEDDIE.

Colloid Milium. Presented by DR. B. F. RYAN.

News and Comment

ANNOUNCEMENTS

Earl D. Osborne Fellowship in Dermal Pathology.—This fellowship, sponsored by the American Academy of Dermatology and Syphilology, is to provide annually for one year the opportunity for study and training in dermal pathology to a postgraduate student who has completed satisfactorily at least two years of training in dermatology or one of its allied branches in accordance with the requirements of the American Board of Dermatology and Syphilology. A stipend of $2,500 will be given to the candidate selected. The period of training will be spent at the Armed Forces Institute of Pathology, Washington, D. C., the appointment being subject to approval by the Director of the Institute. Since the American Board of Dermatology and Syphilology has approved the Institute for one year of training, the time spent will be accredited by the Board. The primary purpose of this fellowship is to train dermal pathologists. The large amount of material in dermal pathology at the Institute will be available for study, and, in special circumstances and with approval, original research may be undertaken under the direction of the chief of the dermal pathology section of the Institute.

Dermatologists in training who are interested may obtain application blanks for the Earl D. Osborne Fellowship from Dr. Hamilton Montgomery, Chairman of the Committee on Pathology of the American Academy of Dermatology and Syphilology, 102-110 Second Ave., S.W., Rochester, Minn. The next appointment available begins July 1, 1954.

CORRECTION

In the article, "Atopic Dermatitis: A Study of Its Natural Course and of Wool as a Dominant Allergenic Factor," by Drs. Earl D. Osborne and Philip F. Murray, in the December, 1953, issue of the ARCHIVES, the authors request that the second sentence of the final paragrpah on page 619 be changed to read as follows: "Eighty-two percent had their onset in the seven cold months (September-March), with an average of 11.7% a month; 18% had their onset in the five warm months (April-August), with an average of 3.6% a month.

Books

Atlas der Haut- und Geschlechtskrankheiten: Hautkrankheiten. By L. Arzt and J. Tappeiner. Four hundred fourteen color reproductions on 116 plates with legends in Latin and an attached booklet of 87 pages in which the salient features of each picture are pointed out in German. Urban and Schwarzenberg, Frankgasse 4, Wien 14, 1953.

This is the second volume of the monumental work by the Austrian dermatologists. The first, which is entirely devoted to syphilis, was reviewed in the A.M.A. Archives of Dermatology and Syphilology in August, 1951 (**64**:254). In the present volume an astounding array of diseases of the skin are portrayed, ranging from the common ones to those of most infrequent occurrence. In some, variety of form is presented in detail; there are 16 illustrations of lichen planus, the rare bullous form being reproduced with surprising fidelity. Exhaustive attention is given also to psoriasis, with 22 different aspects being shown. Changes in the nails are covered widely.

There are many illustrations of commonly encountered dermatoses, reproductions of which in color are rarely published. Representative of such are trichomycosis axillaris, xanthelasma, molluscum contagiosum, milium, seborrheic verruca, and superficial fungous infections, to mention only a few. The less familiar dermatoses, also well-portrayed, include those almost never seen in the United States, of which prurigo of Hebra, melanosis of Riehl, and dermatitis exfoliativa neonatorum of Ritter are examples. Accurate color reproductions of parapsoriasis, of the primary atrophies, Kaposi's disease, the almost forgotten maculae caeruleae, or pseudoxanthoma elasticum have, in the past, been hard to find; this atlas contains many fine specimens, including one of even morbus Sutton (halo nevus).

Of unequaled excellence, in the opinion of this reviewer, are the pictures of trombidiosis, poikiloderma vasculare of Jacobi; maculae caeruleae, arsenical melanoderma, some of the leukemias, and the parapsoriasis group. In some instances a high degree of faithful portrayal was not achieved, as for example, of acute lupus erythematosus, mucosal tuberculosis, dyshidrosis, some of the carcinomas, ecthyma gangrenosum, agranulocytosis, and pemphigus.

The atlas contains also venereal diseases—chancroid, and some of the cutaneous manifestations of gonorrhea.

The use of Latin terms in the legends indicates a trend to eliminate the Greek neuter noun and to substitute a noun of the feminine gender, e.g., sclerodermia circumscripta for scleroderma circumscriptum—a move considered, by this reviewer, to be constructive, since the uniform use of corresponding feminine form of the qualifying adjective would put an end to some of the chronic infractions of the rules of nomenclature.

Considering the magnitude of the effort involved in the production of several hundred pictures in color, it would seem that the minor additional task of having the attached booklet translated into English would be negligible; yet it would make this beautiful atlas more popular among physicians of the English-speaking countries.

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1. Sayer, R. J., et al.: Am. J. M. Sc. *221*:256 (Mar.) 1951.
2. Welch, H.: Ann. New York Acad. Sc. *53*:253 (Sept.) 1950.
3. Werner, C. A., et al.: Proc. Soc. Exper. Biol. & Med. *74*:261 (June) 1950.
4. Wolman, B., et al.: Brit. M. J. *1*:419 (Feb. 23) 1952.
5. Potterfield, T. G., et al.: J. Philadelphia Gen. Hosp. *2*:6 (Jan.) 1951.
6. King, E. Q., et al.: J. A. M. A. *143*:1 (May 6) 1950.

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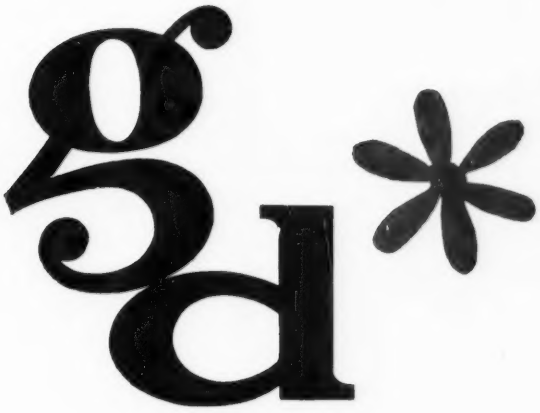

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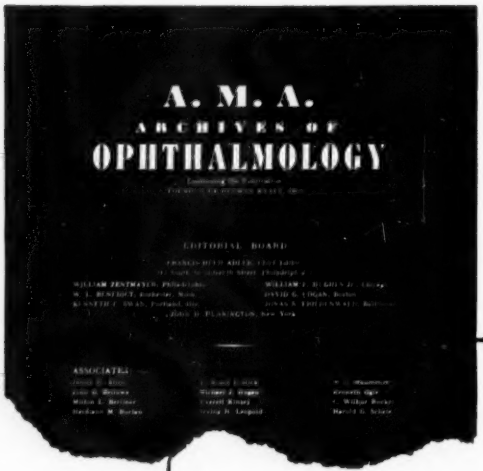

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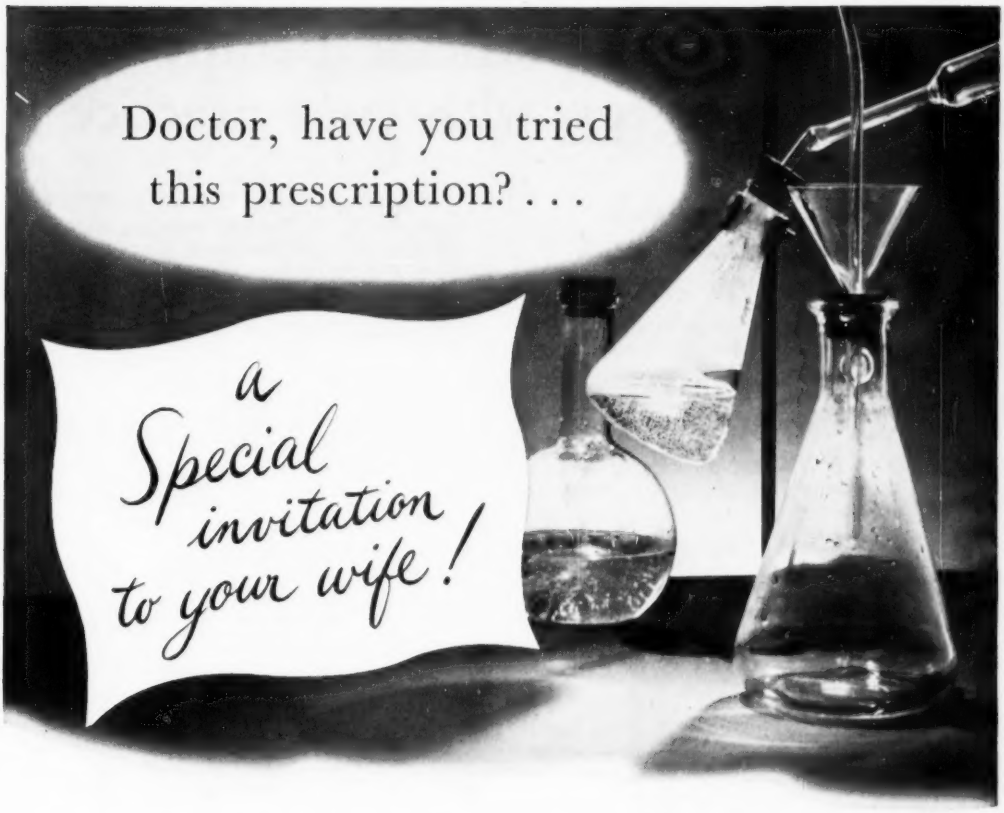

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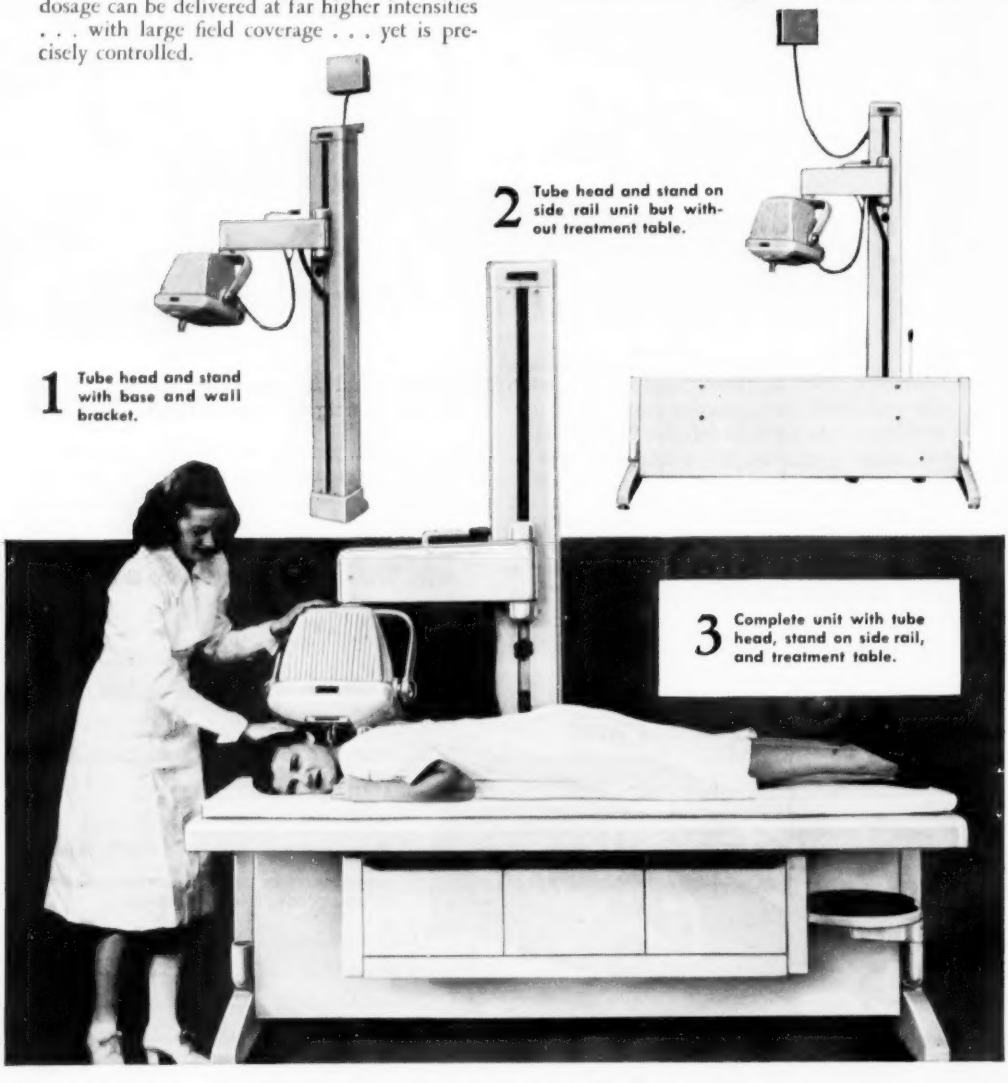

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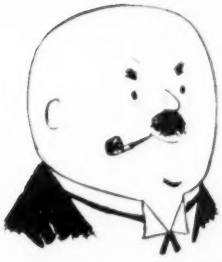

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